

# **Childhood arthritis and osteomyelitis**

## **Incidence and characteristics**

by

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*This thesis is dedicated to my son Oscar Birk*



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# PREFACE

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Øystein R. Riise



## Abbreviations

ACR	American College of Rheumatology
ANA	Antinuclear antibodies
Anti-CCP	Anti-cyclic citrullinated peptide antibody
Anti-DNAse B	Anti-deoxyribonuclease B
ARF	Acute rheumatic fever
ASO	Antistreptolysin-O
AUC	Area under the curve
CI	Confidence interval
CRP	C-reactive protein
CT	Computed tomography
DALY	Disability adjusted life years
DMARD	Disease modifying antirheumatic drug
EIA	Enzyme immunoassay
ELFA	Enzyme-linked fluorescence immunoassay
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GAS	Group A streptococci
HLA	Human leukocyte antigen
HSP	Henoch-Schönlein purpura
IBD	Inflammatory bowel disease
IC	Immunochromatography
ICD	International classification of diseases
IgM	Immunoglobulin M
ILAR	International League of Associations for Rheumatology
JAS	Juvenile ankylosing spondylitis
JCA	Juvenile chronic arthritis
JIA	Juvenile idiopathic arthritis
JPsA	Juvenile psoriatic arthritis
JRA	Juvenile rheumatoid arthritis
MRI	Magnetic resonance imaging
NA	Not assessed
NS	Not statistically significant
OM	Osteomyelitis

OR	Odds ratio
PET	positron emission tomography
PMN	Polymorphonuclear
PSRA	Poststreptococcal reactive arthritis
RA	Rheumatoid arthritis
ReA	Reactive arthritis
RF	Rheumatoid factor
ROC	Receiver operating characteristics
SLE	Systemic lupus erythematosus
<i>S. pyogenes</i>	<i>Streptococcus pyogenes</i>
STIR	Short tau inversion recovery
WBC	White blood cell
WBMRI	Whole-body MRI

## List of Papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

- I Riise ØR, Handeland KS, Cvancarova M, Wathne KO, Nakstad B, Abrahamsen TG, Kirkhus E, Flatø B. Incidence and Characteristics of Arthritis in Norwegian Children: A Population-Based Study. *Pediatrics* 2008;121, e299-e306
- II Riise ØR, Lee A, Cvancarova M, Handeland KS, Wathne KO, Nakstad B, Gaustad P, Flatø B. Recent-onset childhood arthritis-association with *Streptococcus pyogenes* in a population-based study. *Rheumatology* 2008;47,1006-11
- III Riise ØR, Kirkhus E, Handeland KS, Flatø B, Reiseter T, Cvancarova M, Nakstad B, Wathne KO. Childhood osteomyelitis-Incidence and differentiation from other acute onset musculoskeletal features in a population-based study. *BMC Pediatrics* 2008; 8 (1):45
- IV Handeland KS, Riise ØR, Wathne KO, Nakstad B, Flatø B. Predictors of Juvenile Idiopathic Arthritis in a population-based cohort of children with very early arthritis. (Submitted for publication)



# BACKGROUND

## Introduction

The starting point of my interest in this field was an impression that in many children with acute signs of joint swelling or refusal to move an arm or a leg, the parents or the children would refer to a trauma at the onset of the symptoms. In many cases there would also be a history of recent infection.

As toddlers often stumble and fall, a history of trauma may be a coincidence. On the other hand, a fall could be the result of a pathologic joint or bone process or lead to disruption of the endothelium or other mechanisms allowing bacteria to invade the bone.

Children frequently have infections and a recent infection could also be a coincidence; nevertheless infections could cause a bacteraemia followed by osteomyelitis or septic arthritis or activate the immune system so that joint inflammation occurs.

If doctors are consulted they have a challenge whether to “wait and see” or adopt adequate tests and manage further follow-up and treatment. During my first years of training in paediatrics I experienced that the management of these children varied.

I found the search for the location and possible cause of the signs and symptoms as challenging and interesting. Especially, I enjoyed the teamwork that could involve physiotherapists, orthopaedic surgeons, oncologists, ophthalmologists, cardiologists, rheumatologists, infectious disease specialists, microbiologists, radiologists, gastroenterologists and many more.

Arthritis is an inflammation of the synovia of the joints<sup>1</sup>. Osteomyelitis is an infection characterised by inflammatory destruction and new apposition of bone<sup>2</sup>. The presence of inflamed synovia and/or joint effusion adjacent to the site of bone infection may reflect septic arthritis or non-septic arthritis.

Most studies present patients with chronic arthritis, or selected groups of patients with arthritis or osteomyelitis based on retrospective methodology at hospitals or questionnaires to primary care physicians. Retrospective case series from hospitals tend to be biased toward the more ill patients. Studies based on questionnaires may be limited by variability in examination of patients and limited exclusion of other diagnosis.

Epidemiological studies want to describe the natural history and outcome in different disease entities. They may predict early prognostic factors and may help understanding how subgroups of disease present. Differences between regions and time could generate hypotheses regarding environmental and genetic factors. Prospective studies on incidence, disease course, diagnostic tests and sequelae may improve health care management of children with acute onset musculoskeletal features.

## Childhood arthritis

Arthritis in childhood comprises joint infections, post- or parainfectious arthritis, transient arthritis, chronic arthritis or arthritis associated with a wide range of other conditions<sup>3</sup>. The arthritic disease may be migratory, non-migratory, involve one or many joints and may affect other organ systems such as heart, skin and eyes<sup>3-5</sup>. There are classification criteria and several studies on chronic arthritis and acute rheumatic fever (ARF), but little data and no classification criteria for the other types of childhood arthritis<sup>4,6</sup>.

The incidence of arthritis in children has been reported in a Finnish study from 1986 at 109 per 100 000 children, in a German study from 2001 at 83 per 100 000 and in a small Finnish study from 2003 at 64 per 100 000<sup>3,7,8</sup>. However, in the German study the subgroups of arthritis were not explained in detail and the recruitment was based on questionnaires distributed to primary care physicians. Kunnamo *et al* found that 71% had transient arthritis, 17% had chronic arthritis, 6% had septic arthritis and 5% had post infectious arthritis (enteropathic arthritis)<sup>3</sup>.

## Chronic arthritis

Chronic arthritis is the most common chronic rheumatic disease in children. It comprises a heterogenous group of inflammatory disorders that affects joints, bone, muscle and connective tissue and is an important cause of short-term and long-term disability in children<sup>5</sup>. The first classification criteria were proposed by Ansell and Bywaters in 1959<sup>9</sup>. In the 1970s two sets of criteria were proposed: the criteria for juvenile rheumatoid arthritis (JRA) developed by the American College of Rheumatology (ACR)<sup>10</sup> and the criteria for juvenile chronic arthritis (JCA) published by the European League Against Rheumatism (EULAR)<sup>11</sup>. Different classification criteria for juvenile arthritis made a comparison of studies difficult and the Pediatric Standing Committee of the International League of Association for Rheumatology (ILAR) was challenged to develop a new set of criteria in 1993. In 2004 the second revision of criteria for juvenile idiopathic arthritis (JIA) was published<sup>6</sup>. JIA is arthritis of unknown etiology that has persisted for more than six weeks with onset before the age of 16 years<sup>6</sup>. The new criteria classified JIA into the following subgroups: systemic arthritis, oligoarthritis, RF-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, enthesitis related arthritis and undifferentiated arthritis (Table 1).<sup>12</sup>

**Table 1. Comparison of Classifications of Childhood Arthritis\***

Criteria	ACR	EULAR	ILAR
Terminology	Juvenile rheumatoid arthritis (JRA)	Juvenile chronic arthritis (JCA)	Juvenile idiopathic arthritis (JIA)
Basis of classification	Clinical	Clinical and serologic (RF)	Clinical and serologic (RF)
Onset and course	Onset only	Onset only	Onset and course
Age at onset of arthritis	≤ 16 yr	≤ 16 yr	≤ 16 yr
Duration of arthritis	≥ 6 wk	≥ 3 mo	≥ 6 wk
Subgroups	Systemic	Systemic	Systemic
	Polyarticular	Polyarticular JCA	Polyarticular RF-negative
Subgroups	Pauciarticular	Juvenile rheumatoid arthritis	Polyarticular RF-positive
		Pauciarticular	Oligoarticular
Subgroups		Juvenile psoriatic arthritis (JPsA) Juvenile ankylosing spondylitis (JAS) Arthritis of IBD	Persistent
			Extended
Subgroups			Psoriatic arthritis
			Enthesitis-related arthritis
Subgroups			Other arthritis
Excluded subgroups	JAS JPsA Arthritis of IBD		
Exclusion of other diseases	Yes	Yes	Yes

\*based on Textbook of Pediatric Rheumatology. ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; ILAR, International League of Associations for Rheumatology; IBD, inflammatory bowel disease; JAS juvenile ankylosing spondylitis; JPsA, juvenile psoriatic arthritis; RF, rheumatoid factor.

Chronic childhood arthritis has been described in all races and geographical areas; however, its incidence and prevalence vary considerably<sup>13</sup>. A review found that the prevalence was higher in population-based studies and in North American studies. Clinical-based studies were more homogenous in results. Diagnostic criteria or duration of the studies had no impact, although the study sample may have been too small to detect such differences.

The incidence of juvenile chronic arthritis in Finland, Norway and Sweden has been reported at 11-23 cases per 100 000 per year, which is higher than rates reported from other European countries<sup>3, 14-18</sup>. Oligoarthritis represents the most common onset type accounting for 50% to 75% of all cases<sup>13</sup>. More girls than boys are affected, although the sex distribution varies with disease subtype with female to male ratio 2-3 to 1 in the oligo- and polyarticular onset groups, an even distribution of systemic onset arthritis and a male predominance in enthesitis related arthritis<sup>16, 19, 20</sup>. Two major peaks in onset are observed at 1-2 years and 9-15 years of age<sup>14, 16, 21</sup>. The knees are most commonly involved<sup>22, 23</sup>.

Antinuclear antibodies (ANA) are detected in up to 50% of patients with oligoarthritis and they represent a risk factor for iridocyclitis. Rheumatoid-factor-positive polyarthritis is similar to adult RF-positive rheumatoid arthritis and is mainly seen in adolescent girls. Many of these patients also have antibodies against cyclic citrullinated peptide (CCP)<sup>12</sup>. The cause and pathogenesis of JIA seem to include both genetic and environmental components<sup>24, 25</sup>. The first genome-wide scan supports that several genes, including at least one in the HLA region affects the susceptibility to JIA<sup>26</sup>. Many associations between subsets of JIA and HLA or non-HLA molecules have been described<sup>25, 27, 28</sup>. Most patients with enthesitis-related arthritis are reported to be HLA-B27 positive<sup>29</sup>. Newer studies have found that 40-60% of patients have remission at follow-up<sup>5, 14</sup>.

Indicators of poor outcome are severity and number of joints, wrist or hip involvement, presence of RF, persistent active disease and early radiographic changes<sup>30</sup>. The use of steroids can also cause severe growth retardation and osteoporosis<sup>31, 32</sup>.

Only one previous study has focused on identifying clinical and laboratory features that may predict the evolution into chronic arthritis among patients with early onset arthritis. Kunnamo *et al* found that a low CRP value, the absence of fever and an elevated IgG were independent factors for chronic arthritis in patients whose disease duration exceeded two weeks<sup>23</sup>.

### **Post- and parainfectious arthritis**

Post- and parainfectious arthritis comprises a heterogenic group including viral arthritis, acute rheumatic fever (ARF), post-streptococcal arthritis (PSRA) and arthritis following genitourinary tract or gastrointestinal tract infections (reactive arthritis) of a specific organism.

ARF is a connective tissue disease characterised by an inflammatory process that affects several organs of the body. An epidemiological association between *S. pyogenes* and ARF has been established<sup>33</sup>. The Jones Criteria for guidance in the diagnosis of ARF were initially proposed by T. Duckett Jones, in 1944<sup>34</sup>. Committees of the American Heart Association have modified, revised and edited these criteria and the last update came in 1992. The criteria were established to guide physicians in the diagnosis and to minimise its over diagnosis. The major manifestations are carditis, polyarthritis, chorea, erythema marginatum and subcutaneous nodules. The minor manifestations are arthralgia, fever, elevated acute phase reactants, and prolonged PR interval on electrocardiogram. "If supported by evidence of preceding of group A streptococcal infection, the presence of two major manifestations or of one major and two minor manifestations indicates a high probability of acute rheumatic fever"<sup>4</sup>.

Data of high quality on the incidence of ARF are scarce. In developed countries there was a significant decrease after the 1950s. By 1994 it was estimated to be below 1 per 100 000<sup>35</sup>. A few studies from developing countries have estimated an annual incidence of 1.0 per 100 000 in Costa Rica, 72 per 100 000 in Sudan and 150 per 100 000 in China<sup>35, 36</sup>. The annual incidence also differ between population groups within countries such as Samoans and Chinese on Hawaii and Aborigines (> 200 per 100 000) and non-Aborigines in Australia<sup>37</sup>. Determinants of the ARF epidemic are socioeconomic and environmental factors and health-system related factors<sup>38, 39</sup>. In the early 1990s it was said that 12 million people suffered from ARF of whom at least 3 million had congestive heart failure. Although initial attacks of ARF can lead to rheumatic heart disease it is usually the results of recurrent attacks of ARF. The prevalence of rheumatic heart disease peaks at age 25-34<sup>40</sup>. Penicillin treatment and long-term penicillin prophylaxis is recommended in children with ARF<sup>4</sup>.

In 1982 Goldsmith and Long described a post-streptococcal syndrome in children that was characterised by arthritis but was clinically different from ARF<sup>41</sup>. In 1997 Ayoub and Ahmed



proposed criteria for post-streptococcal reactive arthritis (PSRA): A) Characteristics of arthritis: 1. Acute-onset arthritis, symmetric or asymmetric, usually non migratory, can affect any joint. 2. Persistent or recurrent. 3. Poorly responsive to salicylates or non steroidal anti-inflammatory drugs. B) Evidence of antecedent group A streptococcal infection. C) Does not fulfil the modified Jones criteria for the diagnosis of ARF<sup>42</sup>. Most authors have suggested that PSRA is a distinct clinical identity that must be distinguished from ARF, while others consider it to be a part of the spectrum of ARF<sup>41, 43-45</sup>. In PSRA, cardiac disease was present several months after the onset of arthritis in 5.8% of the patients described in the literature<sup>46</sup>. Therefore penicillin treatment and long-term penicillin prophylaxis have been suggested. The proposed duration of prophylaxis varies<sup>47-50</sup>.

The annual incidence of PSRA in Florida was estimated at 1-2 per 100000 children and was twice as frequent as ARF. The mean age was 10 years<sup>49</sup>. The arthritis can last from 5 days to 8 months and some patients continued to have arthralgia for many months after remission. Ahmed *et al* found that PSRA was associated with HLA-DRB\*1<sup>46</sup>. The term reactive arthritis (ReA) has by some authors been used for non-septic arthritis developing after an extra-articular infection with one of the so-called arthritogenic bacteria, particularly *Chlamydia*, *Yersinia*, *Salmonella*, *Shigella* or *Campylobacter*<sup>51, 52</sup>. Reiter's syndrome is a presentation of reactive arthritis defined by the triad of arthritis, conjunctivitis, and urethritis (or cervicitis)<sup>52</sup>.

However, the criteria for ReA used in the literature and in clinical practice have ranged from a short history of undifferentiated arthritis to criteria such as the 1995 Berlin Third International Workshop on ReA,<sup>53, 54</sup> which consist of the presence of a typical peripheral arthritis (a predominantly lower limb, asymmetric oligoarthritis) in addition to evidence of a preceding infection (either a history of diarrhea or urethritis within the preceding 4 weeks or laboratory confirmation of infection with an arthritogenic organism in the absence of clinical symptoms).

*Chlamydia* and enterobacteria arthritis seem to be frequent in Norwegian adult<sup>55</sup>. *Yersinia* arthritis has been found in Finnish and Italian children with arthritis although the risk of reactive arthritis after an enterobacterial infection is probably low<sup>3, 56-58</sup>. Most cases of arthritis following gastrointestinal tract infections occur in boys between the ages of 8 and 12 years, but sex and age distribution vary according to the causative organism.

Lyme arthritis was first described by Steere and colleagues in 1977 in a cluster of children thought to have JRA in and around Old Lyme, Connecticut, USA<sup>59</sup>. The term *Lyme borreliosis* is often used in Europe; *Lyme disease* is the most frequent term in North America. There is no classification criterion for *Lyme borreliosis*. Laboratory methods to document infection with *B. burgdorferi* include direct tests, such as culture or polymerase chain reaction (PCR) to detect borrelia sequences, and indirect tests such as serology.

In Europe *Lyme borreliosis* is probably most common in the in central Europe, but occurs endemically from Scandinavia to the Mediterranean. In Norway, surveillance was initiated in 1991<sup>60</sup>. It is most frequently reported in the counties of Vestfold, Telemark, Aust-Agder, Vest-Agder

and Rogaland. A study from southern Sweden found an annual incidence of Lyme borreliosis of 69 per 100 000 (paediatric and adult population). In children Lyme borreliosis was most common in patients aged 5-9 years. Lyme arthritis was present in 7% of all cases <sup>61</sup>.

Arthritis may appear months to years after infection <sup>62</sup>. Monarthritis of a knee occurs in two thirds of children. At onset the arthritis could last for few days, but recurrent episodes, and more than 3 months disease duration has been reported in up to one fifth of patients. The American Academy of Pediatrics recommends 28 days of antibiotic treatment and additional therapy in case of recurrent attacks <sup>50</sup>.

When we started our study there were few reports of the incidence of childhood arthritis such as enteropathic, Lyme or PSRA <sup>7, 49, 62</sup>.

The impact of viruses in acute and chronic arthritis is complex, because all children are occasionally inflicted by viral microbes. Arthralgia is probably more common than arthritis and remission occurs within a few days. Togaviruses (rubella, alphaviruses) account for most cases <sup>63, 64</sup>. Studies of viral serology in children with chronic arthritis have been hard to interpret. Do the patients have chronic arthritis with concomitant viral infection or is the virus responsible for the arthritis? An argument that supported the rubella virus as a potential cause of chronic arthritis was the presence of rubella virus in the synovial fluid of several chronic arthritis patients <sup>65</sup>. For hepatitis B and C, arthritis may result from host cellular or humoral immune responses, while other viruses may act indirectly by altering the integrated host defence network, or by inducing frank autoimmunity, as with human immunodeficiency virus (HIV) and human T-cell lymphotropic virus type 1 (HTLV-1) <sup>63</sup>. The association between rubella and other viruses in chronic arthritis remains unsolved <sup>64, 66</sup>.

Since the HIV epidemic began, millions of people in sub-Saharan Africa have been infected. This is also reflected in departments of Rheumatology. A study from adult patients in Congo-Brazzaville showed that 22% of the patients were HIV positive and that 80% of these patients had HIV-related arthritis <sup>67</sup>.

Kunnamo found that three children had arthritis associated with a recognised viral infection; measles, varicella and adenovirus <sup>3</sup>. In another population based Finnish study three children had antibodies against Sindbis (Pogosta) virus <sup>8</sup>.

### **Transient arthritis**

The term “transient” arthritis is most known from the idiopathic disorder “transient or toxic synovitis of the hip.” It is characterised by short disease duration without a recognised microbe although a history of recent-upper airway infection is present in several patients <sup>68</sup>. A study that compared septic arthritis with transient synovitis of the hip found that septic arthritis could be predicted by a history of fever, non-weight-bearing, ESR  $\geq 40$  mm/h and serum WBC  $> 12 \times 10^9$  cells/l <sup>69</sup>. The annual incidence rate of transient synovitis of the hip has been estimated from 39 to

200 per 100 000 subjects<sup>3, 7, 70, 71</sup>. Transient synovitis of the hip is most common in boys aged 3-10 years. One study showed that ten percent of patients had recurrent attacks within the first two years. Legg-Calvé-Perthes, has been reported as long term sequelae<sup>3, 70-72</sup>.

### Septic arthritis

Septic arthritis is usually defined as the presence of bacteria in the synovial fluid by Gram's stain or culture, synovial fluid white blood cell (WBC) count  $\geq 50 \times 10^9/L$  or in some cases by a positive blood culture or culture from other possible sites of infection<sup>3, 69, 73-75</sup>. Septic arthritis is a serious and potentially life threatening disease that can lead to rapid destruction of the articular hyaline cartilage and irreversible loss of joint function<sup>76, 77</sup>. It most frequently results from haematogenous spread of bacteria, although it can also occur due to local spread from contiguous infection (i.e. osteomyelitis), trauma or surgery. Studies have shown that the diagnosis is delayed in 31% to 48% of children<sup>78, 79</sup>.

In one study septic arthritis had an annual incidence of 6.7 per 100 000 children<sup>3</sup>. An increase in the incidence has been suggested, but was not confirmed in another study<sup>80-82</sup>. It is slightly more common in boys than in girls and is most common in the youngest children<sup>75</sup>. In neonates *group B Streptococci* is most common followed by *S. aureus*. *S. aureus* remains the most common organism in older children, followed by *S. pneumonia* and *S. pyogenes*. However, *Kingella kingae* has been reported more frequently in recent studies and *H. influenzae* has become rare in countries where *H. influenzae* vaccination programs are used<sup>74, 83</sup>.

There is limited data on the incidence of septic arthritis in sub-Saharan Africa, but *Salmonella* was cultured in 40% to 60% of children from series in Zambia, Malawi and Kenya<sup>84-86</sup>. This is probably linked to the assumption that *Salmonella* is the most common organism found in the blood of sub-Saharan children<sup>87-89</sup>.

The proportion of positive synovial fluid cultures in children diagnosed with septic arthritis is reported at 30% to 82%. A positive microbiological finding is often used as a selection factors which therefore overestimate the number of culture positive cases. Culture positive and culture negative patients have been found to be similar in terms of age, joint involved, synovial fluid WBC count and ESR value<sup>75, 82, 90, 91</sup>. Possible explanations for negative joint cultures are that pus exerts a bacteriostatic effect on microbiological growth, prior use of antibiotics and culture techniques<sup>91</sup>. The joints of the lower extremity (hip, knee, and ankle) are most commonly involved whereas septic arthritis affecting the small joints of the hands and feet is rare<sup>80, 90</sup>. In a few patients more than one joint is infected<sup>82</sup>.

## Childhood osteomyelitis

Osteomyelitis is an infection of bone that is usually bacterial in origin <sup>92</sup>. Osteomyelitis may cause growth changes or pathological fractures <sup>93, 94</sup>. It can be limited to a single portion of the bone or can involve several regions, such as marrow, cortex, periosteum, and the surrounding soft-tissue <sup>2, 95, 96</sup>. A suggested classification of different types of OM is shown in table 2<sup>97</sup>. Haematogenous osteomyelitis is most common in children.

**Table 2. Suggested classification of osteomyelitis (OM)**

Haematogenous osteomyelitis
- acute
- subacute
- chronic
Exogenous osteomyelitis
- posttraumatic
- postoperative
- contiguous
<b>Osteomyelitis of unknown aetiology (sterile lesions)</b>
- primary chronic sclerosing
- chronic recurrent multifocal (CRMO)
- SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis)

In the metaphysis there are tiny vascular loops in which blood flow is sluggish and oxygen tension is low. In the pathogenesis of haematogenous OM there are three main mechanisms. 1) A local circulatory disturbance caused by bacterial inflammation (or a minor trauma) leading to thrombosis of the sinusoidal vessels; 2) increased pressure in the medullary cavity due to exudation and later a polymorphic inflammatory response, producing massive bone necrosis and 3) a destructive proteolytic effect of pus <sup>97</sup>.

In the first year of life blood vessels connect the metaphysis and epiphysis so that pus from the metaphysis can enter the joint space. In older children the purulent material moves laterally through cortical vascular channels and ends up under the periosteum.

*Staphylococcus aureus* is the most common microbe followed by *S. pyogenes* and group *B streptococcus*. Series have shown that the proportion of culture-negative osteomyelitis cases has ranged from 15% to 47%. <sup>94, 98</sup> Two retrospective studies have shown a higher proportion of negative culture results in children with longer duration of symptoms and older age <sup>94, 98</sup>. One study comparing culture negative and culture positive patients found that both groups responded similarly to treatment and therefore recommended management as presumed *S. aureus* disease in culture-negative cases <sup>98</sup>. Histology showing pathologic changes is an important asset in subacute and chronic osteomyelitis patients <sup>99</sup>.

The incidence of osteomyelitis has been reported from retrospective hospital based studies or from national patient registries at 3 to 72 per 100 000. Vertebral osteomyelitis has an annual incidence of < .5 per 100 000 or a proportion of 2% of all osteomyelitis cases <sup>94, 100-105</sup>. Blyth *et al.* found a reduction of the incidence in Scotland of more than 50% between 1979 and 1997 and an

increase in the proportion of patients with subacute osteomyelitis (a history of more than two weeks at presentation to hospital). Femur and tibia have been the most frequently affected bones<sup>93, 102, 103, 105</sup>. Blyth *et al.* also suggested a lower proportion of patients with long-bone involvement<sup>103</sup>. Most studies report that osteomyelitis is more frequent in boys than girls, however; this was not found in a previous Norwegian study<sup>93, 103, 105</sup>.

According to some authors discitis is inflammation restricted to the disc space and the term spondylodiscitis is used where both the disc and the adjacent bone structures are affected. The distinction of vertebral disc infection from vertebral osteomyelitis was originally a radiological distinction, however, even with modern imaging techniques, there is no accepted basis on which how to make such a distinction<sup>106</sup>. In children vascular channels penetrate into the nucleus pulposus helping bacterial emboli to be deposited within the disc itself. It is thought that the abundant intraosseous arterial anastomosis both predispose to an infective agent settling in the disc, as well as promoting clearance of microbes and allowing a more rapid resolution of infective discitis than that which is observed in adults<sup>107, 108</sup>. *S. aureus*, *Enterobacteriaceae* and *Moraxella* are the microbes most commonly identified in patients with discitis. Brown *et al.* do not recommend open or needle disc biopsies in young children because of a low rate of positive cultures and unknown long-term effect of the procedure. They as well as other authors only suggest disc biopsies in the immunocompromised child or those that do not respond to antibiotics<sup>108-110</sup>. Not all centres routinely prescribe antibiotics<sup>110</sup>. However, a retrospective multicentric study demonstrated a significant reduction in the duration of symptoms in those treated with iv. antibiotics compared with oral or no antibiotics<sup>106</sup>.

## Identification of arthritis and osteomyelitis patients

### Clinical

Care of a child with musculoskeletal complains requires time and a complete paediatric examination<sup>111</sup>. A child with arthritis or osteomyelitis may appear well<sup>12, 103</sup>.

### Laboratory tests

No laboratory test can confirm the diagnosis of arthritis, although tests can support the evidence of inflammation. Patients with chronic arthritis may have normal values<sup>23</sup>. In patients with acute osteomyelitis ESR, CRP and WBC are elevated in 92-100%, 82-98% and 35-58% of the cases respectively<sup>112, 113</sup>. However, acute phase reactants can be normal when bone abscesses are present<sup>93, 94, 114</sup>. The discriminative ability of laboratory tests to identify osteomyelitis patients in an unselected cohort of children with acute onset musculoskeletal features has previously not been studied.

### **Plain films**

Plain films use ionising radiation and should be the first step in the imaging assessment of osteomyelitis. Plain films can also be used in patients with suspected septic or persistent arthritis. They mostly exclude fractures or other orthopaedic conditions and provide landmarks for other imaging modalities. The earliest sign in osteomyelitis is the swelling of deep soft-tissue. Bone destruction or periosteal reactions are found 10-21 days after the onset of disease <sup>115</sup>. Radiographic damage in chronic arthritis patients are observed after 6 to 10 years <sup>116</sup>.

### **Ultrasound**

Ultrasound is useful for evaluation of synovitis, joint effusions, tenosynovitis and ganglion cysts and guides fluid aspiration. Hip joints and shoulder joints can be difficult to demonstrate clinically <sup>111, 117</sup>. However, ultrasound is user dependent and requires experience. Although that a normal ultrasound can not rule out osteomyelitis findings as deep soft tissue swelling, elevation of periosteum by fluid, subperiosteal abscess and costical erosion may support the diagnosis <sup>118</sup>.

### **Computed tomography**

Computed tomography (CT) uses ionising radiation and generates a three dimensional image from a large series of two dimensional radiographic images. CT can be of use in evaluation of osteomyelitis, sacroiliac joints, temporomandibular joints and feet, but is used less frequently after the introduction of MRI <sup>12</sup>. CT is said to be superior to other imaging modalities in evaluation of chronic osteomyelitis patients as it demonstrates cortical erosions and bone sequestration. It is also useful to guide biopsy procedures. <sup>119, 120</sup>

### **Bone scan**

Bone scan could be used if there is doubt about osteomyelitis or the location of a pathological bone process. Several types of nuclear imaging modalities exist (e.g. Gallium scan, white blood cell scan, immunoglobulin scan). <sup>99m</sup>Tc methylene diphosphonate (<sup>99m</sup>Tc-MDP) is the most used method for identifying osteomyelitis. The standard approach is a three-phase procedure to examine perfusion, soft-tissue blood pool and delayed (3 hours) bone uptake. Increased uptake on both sides of a joint can provide evidence of arthritis <sup>12</sup>. The intensity of bone uptake becomes more focal at the area of interest, and when positive on all three phases, is highly sensitive for osteomyelitis. Bone scans are reported to be sensitive in the diagnosis of osteomyelitis (73% to 100%), <sup>121-124</sup> but the difficulty in separating bone-marrow processes from soft-tissue disease limits specificity and accuracy <sup>125</sup>.

## MRI

Magnetic resonance imaging (MRI) does not rely on ionising radiation, but on radio waves and magnetisation. The patient is placed in a magnet; a radio wave is sent and then turned off. The patient emits a signal which is received and used for reconstruction of the picture. T1 and T2 are time parameters that depend on physical and chemical properties that vary with the different tissues and are related to the molecule mobility. T1 describes the time required for magnetisation build-up. T2 describe the time for transverse relaxation.

At birth the bone marrow is haematopoietic, during childhood it transforms to fatty tissue at different time in the different bones. Normal red marrow show low signal intensity on T1 and variable intensity on T2. In contrast normal yellow marrow show high signal intensity on T1 and intermediate intensity on T2. MRI shows the overall concentration of fat and water in the marrow rather than its histological changes<sup>126</sup>.

Sequences as STIR (short tau inversion recovery) and T2 fast spin echo can by suppressing the signal from fat better bring out and delineate edematous areas with higher signal intensity than the surrounding tissue as in osteomyelitis and tumours. The T1 fast spin echo with fat saturation will when using MRI contrast media as Gadolinium in the same way bring out and delineate contrast enhanced tissue as in inflammation.

In the acute phase of osteomyelitis, the edema and exudate within the medullary space produce an ill-defined low-signal intensity area on the T1-weighted images and a high signal intensity area on T2-weighted and STIR sequences. The STIR pulse sequence is said to have a negative predictive value for osteomyelitis approaching 100%<sup>125, 127</sup>, however, conventional T1- and T2-weighted images often provide better spatial resolution that better differentiate abscesses from circumscribed soft tissue edema.

Bone marrow findings of acute osteomyelitis on MRI are non-specific, and clinical correlations and risk factor consideration are important to achieve the most correct diagnosis. Compared to acute osteomyelitis, subacute and chronic osteomyelitis often shows a relatively sharp and better defined interface between normal and abnormal marrow<sup>128</sup>. These abscesses may show a rim of low signal intensity. The “rim sign” appears as a low signal intensity rim on T1-wighted SE, T2-weighted SE, and STIR images which correspond to an area of fibrous tissue or reactive bone<sup>127</sup>. Sensitivity of MRI in the diagnosis of osteomyelitis in adults and children is reported at 88% to 100% with specificity of 75% to 100%<sup>125, 127, 129-132</sup>. In some cases subacute osteomyelitis can be difficult to differentiate from bone tumours.

Contrast enhanced MRI is the most sensitive method to determine whether arthritis is present and identify early joint damage. Bony erosions are detected before they are seen on plain radiographs<sup>111, 133</sup>.

The disadvantages of MRI are that small children will require general anaesthesia, imaging of the whole body is inappropriate, and the examination is time consuming and expensive. In all

imaging modalities where contrast fluid is used there is a small risk of life threatening allergic reactions.

As far as we know, MRI has not been used to identify osteomyelitis patients in a large prospective population-based study.

### **Synovial fluid**

Synovial fluid is present in small amounts in a normal joint for lubrication and nutrition. The colour is yellow or clear, the WBC count is  $< .2 \times 10^9/L$  and the polymorphonuclear leukocyte (PMN) ratio is  $< 25\%$ . In septic arthritis the fluid is turbid and serosanguineous, the WBC count can be 25 to  $300 \times 10^9/L$  and the PMN ratio  $> 75\%$ . The proportion of positive synovial fluid cultures varies in patients with septic arthritis (79-36%). A Gram stain can be positive in up to 50% of previously untreated cases<sup>80, 82, 134</sup>. In JIA patients the WBC count can be 15 to  $20 \times 10^9/L$ <sup>12</sup>.

### **Bone biopsy**

If bone biopsy is assessed in patients with suspected osteomyelitis both histological and microbiological samples should be taken due to the low proportion of positive cultures (40-87%)<sup>93, 135, 136</sup>. Prior use of antibiotics, small tissue volumes and sampling errors may be explanations for culture negative results. Histology may show acute inflammatory cells, congestion of small vessels and necrosis. In chronic osteomyelitis patients there can be high numbers of lymphocytes, histiocytes and plasma cells in the absence of neutrophils<sup>137</sup>.

Tissue sampling can be obtained with open surgical biopsy as the golden standard or by fine-needle aspiration (FNA) or core-needle biopsy. The size and number of specimens that should be obtained for histopathology are not known<sup>138, 139</sup>.



## AIMS OF THE STUDY

The overall aim of this study was to estimate the annual incidence of arthritis and osteomyelitis in children, to describe the role of patient characteristics, joint involvement, auto-antibodies, HLA-B27 and microbiological variables in early recognition of subgroups of arthritis patients and evaluate features that identify osteomyelitis patients.

Within this our aims were:

- I We wanted to estimate the annual incidence rate of arthritis in children in urban and non-urban counties and describe the role of patient characteristics, auto-antibodies, HLA-B27, and microbiological variables in early recognition of distinct subgroups of childhood arthritis (paper I).
- II We wanted to investigate the frequency of *S. pyogenes* in a cohort of children with recent-onset arthritis. We wanted to compare the characteristics and early disease course of PSRA patients with those of transient arthritis and juvenile idiopathic arthritis (JIA) and describe the role of patient characteristics, disease duration, auto antibodies and HLA-B27 in the early identification of PSRA. We also wanted to report the occurrence of cardiac involvement during the first 18 months of disease duration in patients with ARF and PSRA (paper II).
- III We aimed to assess the annual incidence rate of different types of osteomyelitis in children and compare the patient and laboratory characteristics in osteomyelitis with that of patients who had other acute onset musculoskeletal features. In addition, we wanted to compare the patient, clinical, microbiological and MRI characteristics of children with acute- and subacute osteomyelitis (paper III).
- IV We wanted to determine the predictive value of patient characteristics, disease variables and routine laboratory features in separating patients with JIA from other types of recent-onset arthritis on an early stage (paper IV).

# MATERIALS AND METHODS

## Study design

Our study is a prospective and partly retrospective population-based study of a cohort of patients with acute onset musculoskeletal features who live in the counties Oslo, Akershus and Buskerud. The patients were examined on admission, after six weeks, six months and thereafter as long as clinically needed. Patients with PSRA were also examined after 18 months (paper II).

## Patients

Patients were recruited from primary care physicians, pediatricians, orthopaedic surgeons and rheumatologists in the counties of Oslo, Akershus and Buskerud. They received four letters: one at the beginning and then every 3 months during the study period. The letters included the recruitment criteria, the referral process to have the patient admitted within one to three days, and informed about arthritis and osteomyelitis in children as well as the objectives of the study. Furthermore, the physicians at the hospitals and at emergency wards were informed through meetings. Patients < 16 years of age with residence in the counties were admitted at one of the paediatric departments in the region or at the regional department of rheumatology (i.e. at Akershus University Hospital, Buskerud Hospital, Ullevål University Hospital or Rikshospitalet Medical Centre). The total number of patients in the region was 255 303 on January 1, 2004<sup>140</sup>. The recruitment period was from 1 May 2004 to 30 June 2005. At the end of the study, we searched the hospitals' computerized records for 181 relevant diagnoses [based on the International Classification of Diseases, 10th edition (ICD 10)]<sup>141</sup> to identify any patients who met the recruitment criteria but had not been included. The last patient data was collected in May 2007.

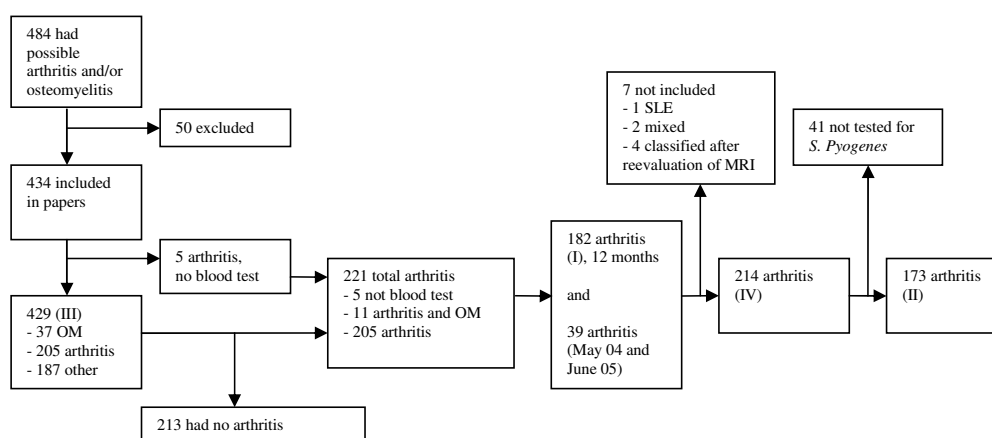
## Recruitment criteria

The recruitment criteria were patients with possible or evident arthritis and/or osteomyelitis, determined on the basis of  $\geq 1$  or more of the following characteristics: (1) joint swelling; (2) limited range of motion in  $\geq 1$  joint, or walking with a limp or other functional limitations affecting arms and/or legs; and (3) pain in  $\geq 1$  joint or extremity together with C-reactive protein (CRP) level of  $> 20\text{mg/L}$  and/or erythrocyte sedimentation rate (ESR)  $> 20\text{mm/hour}$  and/or white blood cell (WBC) count of  $> 12 \times 10^9/\text{L}$ . These signs should have lasted for  $< 6$  weeks and should not have been caused by trauma.

## Inclusion criteria

The inclusion criteria for arthritis patients were one of the following three signs: (1) swelling of a joint; (2) restricted mobility of a joint with warmth and/or tenderness and/or pain<sup>1</sup>; or (3) arthritis demonstrated by ultrasound or magnetic resonance imaging (MRI).

The inclusion criteria for osteomyelitis patients were characteristic signs and symptoms of bone infection and one of the following: (1) positive culture from bone biopsy and/or histology showing inflammation; (2) MRI findings consistent with osteomyelitis; and (3) positive bone scan if bone biopsy and/or MRI were not done. A flowchart showing the patients included in the different papers is presented in figure 1.



**Figure 1. Flowchart showing the patients included in the different papers.** In paper I the patients were included between June 2004 and May 2005. In paper II-IV the patients were included between May 2004 and June 2005. In paper III patients without arthritis and/or osteomyelitis were also included. In that paper the MRIs were evaluated by two radiologists blinded to clinical information. Roman numbers refers to number of paper. OM = osteomyelitis, MRI = magnetic resonance imaging, SLE = systemic

## Exclusion criteria

Patients who had sickle cell anaemia, malignant disease or had been diagnosed with JIA before 1 May 2004 were excluded. In addition patients who had inflamed synovia related to trauma were excluded.

## Non participants

In paper II and III there were 9-20% non-participants due to incomplete data. The non-participants were comparable to the participants as regards age, sex and duration of symptoms. We do not know whether any primary care physicians refused to refer patients to our study.

## Follow-up

In paper III 40-61% of the patients without osteomyelitis did not receive follow-up at six weeks or six months (table 3). According to the hospital medical charts, these patients did not have further symptoms of arthritis or osteomyelitis. In paper I 20% of the arthritis patients did not attend the six weeks follow-up visit and 39% did not attend the six month follow-up visit. Our impression was that parents of arthritis patients who went into remission within few days after the onset of symptoms were less willing to attend the planned follow-up visits.

**Table 3. Follow-up of the patients in the different papers\***

Paper	No. of patients	Follow-up 6 weeks (%)	Follow-up 6 months (%)	Follow-up 18 months (%)
Paper I	182	80	61	NA
Paper II	173	87	69	90 (PSRA)
Paper III	429	97	89	NA
- OM				
- not OM		60	39	
Paper IV	214			
- JIA		100	98	NA
- Infectious		93	93	NA
- Transient/post-infectious		73	50	NA

\* patients with persistent signs or symptoms received up to three years of follow-up  
OM = osteomyelitis; JIA = juvenile idiopathic arthritis; PSRA = poststreptococcal reactive arthritis

## Clinical data

Clinical information was obtained by medical record reviews and physical examination. The number of swollen, tender and mobility restricted joints was registered at each visit. Most arthritis and osteomyelitis patients were examined by one of two physicians (ØR, KH) at six weeks and six months and in addition most patients with JIA were examined by a consultant in paediatric rheumatology (BF).

## Laboratory data

Hemoglobin, WBC with differential, platelet count, ESR, CRP, culturing of throat swab and feces were measured by standard methods. Serologic examinations were assessed by the methods in use at each hospital i.e. antistreptolysin-O (ASO), anti-deoxyribonuclease B (anti-DNAse B), *Hepatitis B*, *Mycoplasma pneumoniae*, *Chlamydia*, *Epstein-Barr*, *Cytomegalovirus*, *Parvovirus B19*, *Yersinia enterocolitica*, *Borrelia burgdorferi*. Antinuclear antibody (ANA) was measured by fluorescence or ELISA, anti-cyclic citrullinated peptide antibody (anti-CCP) by ELISA, IgM RF by ELISA or immunonephelometry and HLA-B27 by flowcytometry, serology or genetic methods. One ANA titre of  $\geq 40$  or a ratio of  $> 1.4$  was considered positive. In addition anti-CCP level of  $\geq 25$  U,  $> 5$  IU/ml, or RF of  $\geq 24.0$  IU/ml was considered positive.

Joint aspiration was recommended within three days if mono- or oligoarthritis of < 2 weeks' duration occurred in combination with one of the following four: 1. fever > 38.5° C, 2. CRP > 30 mg/L or ESR >30 mm/hr or WBC > 12x10<sup>9</sup>/L, 3. excessively painful joint or bone, 4. other suspicious factors for septic arthritis or osteomyelitis. In addition we recommended that joint aspiration should be performed within 14 days if arthritis in one to three joints persisted for more than one week. In paper I the classification criterion for septic arthritis was that either the synovial fluid was positive for bacteria by culture or microscopy, or the synovial fluid WBC count was > 50x 10<sup>9</sup>/L. In paper IV a positive blood culture also classified for septic arthritis.

## **Radiological examinations**

Standard radiographs of the affected area were obtained in all patients by conventional technology except for patients with transient synovitis of the hip with disease duration of less than one week.

An ultrasound of affected joints was performed on admission. In addition an ultrasound of the hips was performed on all of the children <5 years of age with symptoms from the legs.

Three-phase bone scan (<sup>99</sup>Tc methylene diphosphonate) was recommended if there was doubt about the localisation of the arthritis/osteomyelitis.

MRI was recommended within 3 days if mono- or oligoarthritis of < 2 weeks' duration occurred in combination with one of the following four: 1. fever > 38.5°C; 2. CRP > 30 mg/L or ESR >30 mm/hr or WBC > 12x10<sup>9</sup>/L; 3. excessively painful joint or bone; 4. other suspicious factors for osteomyelitis or septic arthritis. We also recommended that MRI should be performed within 14 days if arthritis persisted for more than one week in one to three joints.

In paper I, II and IV we used the standard descriptions from the radiologists as diagnostic tools. However, in paper III two experienced radiologists retrospectively evaluated the MRIs, blinded to all clinical information except for the patient's age and that there was clinical suspicion of osteomyelitis. The MRI findings were presented by consensus.

In cases of bone marrow edema, subacute osteomyelitis was defined as well-circumscribed lesions with homogeneous or peripheral contrast enhancement, periosteal inflammation, fibrosis, fistula or sequester. Acute osteomyelitis was defined as a poor interface between the normal and diseased bone marrow. The radiologists also reported the presence of arthritis in a nearby joint, other soft tissue abnormalities, and other orthopaedic conditions.

The MRIs were performed in different machines in different hospitals (1.0T or 1.5T). The MRI examinations had at least one T1 spin echo sequence and one STIR (Short T1 Inversion Recovery) sequence. In most cases (and in every case with well circumscribed lesions), there was also at least one contrast-enhanced T1 spin echo sequence.

One of the radiologists was then informed of the final diagnosis, and evaluated the follow-up plane radiographs and/or MRIs of the osteomyelitis patients in order to report the presence of any remaining signs or sequelae.

## Classification of patients

Two researchers (ØR, KH) recorded the clinical information on a standardised form. In case of disagreement, the classification was established in consultation with specialists in paediatric infectious diseases (KOW) and paediatric rheumatology (BF).

In paper I we presented all the microbiological data available from admission and at six weeks follow-up when we classified the arthritis patients. However, when we focused on the presence of *S. pyogenes* (paper II) we focused on data from admission and 5 PSRA patients were reclassified to transient arthritis (these patients did not have carditis after 18 months). This was done to increase the likelihood of an association between presence of *S. pyogenes* and arthritis. The arthritis would probably be present 2-4 weeks after infection with *S. pyogenes* and the antibodies would reach their maximum at the time of the onset of arthritis or shortly thereafter (ASO maximum 3-6 weeks after infection with *S. pyogenes* and anti-DNAse B maximum 4-8 weeks after infection with *S. pyogenes*)<sup>4</sup>. If this is the case, the convalescent serum samples would probably not show elevated titres six weeks after the onset of arthritis (8-10 weeks after the estimated infection with *S. pyogenes*). We also changed the anti-DNAse cut-off titre from  $\geq 600$  IU/ml (paper I) to  $\geq 800$  IU/ml in paper II. This was done because anti-DNAse may stay elevated for many months after a streptococcal infection, and because the cut-off titre chosen in paper I was lower than in most other papers on PSRA<sup>32, 43, 48, 142, 143</sup>.

We used MRI as one of the diagnostic tools for identification of arthritis or osteomyelitis patients in all papers. Four patients were reclassified into osteomyelitis in paper III as radiologists retrospectively evaluated the MRIs. In paper I, II and IV we used the routine description from the hospitals' radiologists.

One patient who was classified as JIA in paper I, II and III was excluded in paper IV due to reclassification to SLE. One patient was classified as transient arthritis in paper I, II and III, but was excluded in paper IV due to recurrent fever, highly elevated CRP (415 mg/L) and possible pneumonia or pyelonephritis. One patient with post-infectious arthritis was regrettably missing in paper IV.

## Ethics

Written informed consent was obtained from the parents of the children included in the study. Children aged more than 12 years received a simplified information letter. The Regional Ethics

Committee for Medical Research and the Ombudsman for Privacy in Research at the Norwegian Social Science Data Services approved the study.

## Statistics

All of the analyses were performed by using SPSS 13,14 and 15 for Microsoft Windows (SPSS Inc, Chicago, IL). P-values < .05 were considered statistically significant, except for multiple comparisons in paper III ( $p < .01$ ).

Relations between categorical variables were studied using the chi-square test or Fisher's exact test, for groups composed of < 5 case subjects. Differences between groups for continuous variables were tested using independent samples t-test when variables were normally distributed. For not normally distributed continuous variables we used the Mann-Whitney-Wilcoxon test for comparison between two groups and the Kruskal-Wallis test for comparison between multiple groups. The continuous variables were described in terms of range, medians and quartiles. We constructed 95% confidence intervals for incidence using the normal distribution approximation (paper I).

Two multiple logistic regression models were fitted in order to investigate whether hip arthritis and active disease at six weeks were independently associated with PSRA versus JIA, and whether age and active disease at six weeks were independent predictors of PSRA versus transient arthritis (paper II). Sensitivity was defined in terms of the proportion of positives correctly identified by the test. Specificity was defined in terms of the proportion of negatives correctly identified by the test. Positive predictive value was defined in terms of the proportion of patients with positive test results who were correctly diagnosed. Negative predictive value was defined as the proportion of patients with negative test results who were correctly diagnosed (paper II and III).

The sensitivities and specificities of the laboratory tests used to discriminate between patients with and without osteomyelitis were presented graphically using ROC curves. The area under the ROC curve (ROC AUC) provides a measure of the overall discriminative ability of the test. AUC equals .5 when the ROC curve corresponds to random chance and 1.0 when there is perfect accuracy (paper III).

Logistic regression (Binary logistic) analyses with JIA-diagnosis as the dependent variable were used to identify predictors of JIA (paper IV). Initially, potential predictors of JIA were tested in a univariate model. Continuous variables (except for age) were dichotomized to categorical variables in order to give them a more meaningful value in a clinical setting. This applied to duration of symptoms (cut-off 14 days), temperature (cut-off 38.0 degrees Celsius), neutrophile WBC-count (cut-off  $6.0 \times 10^9/L$ ) and platelet-count (cut-off  $390 \times 10^{12}/L$ ). The cut-off values for the blood tests were based on normal values in our labs.

Variables associated with JIA (p-values below 0.10) in the univariate analysis were analysed as possible predictors in the subsequent multivariate analyses except for total WBC-count that was not included due to a high correlation with neutrophile WBC-count (Pearson correlation 0.8,  $p=0.01$ ) and polyarthritis that was excluded due to high correlation with small-joint involvement (Pearson-correlation 0.54,  $p=0.01$ ). Furthermore, HLA-B-27 and ANA were excluded in the multivariate analyses due to a high percentage of missing values.

When identifying determinants that differentiated the JIA-group from the infectious arthritis group, the numbers of independent variables included in the multivariate analysis were limited due to the low number of patients. We chose two variables for joint distribution (hip and knee), one clinical (fever), one laboratory-variable (neutrophile WBC-count) and one symptom-variable (duration of symptoms) in addition to age and gender.

In the multivariable regression analyses the missing values were replaced with mean values when data were symmetrically distributed and median values when not. Five variables had missing values, ranging from 2.3% to 11.7%.



## SUMMARY OF RESULTS

### Paper I

#### **Incidence and Characteristics of Arthritis in Norwegian Children: A population-Based Study**

We wanted to assess the annual incidence rate of arthritis in children and describe early disease and patient characteristics, microbiological features, and immunogenic factors in children with different subgroups of childhood arthritis. Physicians were asked to refer their patients with suspected arthritis and the patients were assessed on the basis of clinical, radiological and laboratory examinations at inclusion and followed-up at six weeks and six months.

We found a total annual incidence of 71 per 100 000 children. Arthritis was more common in patients younger than 8 years of age and more common in boys than girls under 8 years of age. Transient arthritis was by far the most frequent subgroup, followed by JIA, post-infectious arthritis and infectious arthritis. Children with septic arthritis were younger (median 1.9 years) than those in the other groups and patients with post-infectious arthritis had the highest age of onset (median 7 years). JIA was associated with female gender, polyarthritis, small joint arthritis, absence of hip joint arthritis, ANA, anti-CCP, IgM RF and HLA-B27. PSRA was found in 10% of patients, while arthritis associated with enteropathic bacteria was found in two patients. Eight patients tested positive on viral antibodies. Viral antibodies were found in all diagnostic groups. Three patients had Lyme arthritis.

### Paper II

#### **Recent-onset childhood arthritis-association with *Streptococcus pyogenes* in a population-based study**

In this study we wanted to assess the frequency of signs of *Streptococcus pyogenes* in children with early arthritis, compare the characteristics in patients with post-streptococcal ReA (PSRA) with those in patients with other types of arthritis, and describe the occurrence of carditis in PSRA and ARF. A total of 173 arthritis patients were tested for the presence of *S.pyogenes*. The PSRA patients were examined by a paediatric cardiologist at 18 months.

The percentage of positive streptococcal tests correlated with the age of the child and was found in 35 % of the arthritis patients aged eight to 11 years. Patients with PSRA were older and had a longer disease duration than those with transient arthritis. Hip involvement, inactive disease

at six weeks and six months and negative ANA and HLA-B27 were more frequent in PSRA than in the JIA patients. One third of the patients with PSRA still had signs of streptococcal infection after 18 months. Carditis was only found in one child, who had ARF.

## **Paper III**

### **Childhood osteomyelitis- Incidence and differentiation from other acute onset musculoskeletal features in a population-based study.**

The aim of this study was to assess the annual incidence of osteomyelitis in children, describe the patient and disease characteristics in those with acute (< 14 days disease duration) and subacute osteomyelitis ( $\geq$  14 days disease duration), and differentiate osteomyelitis patients from those with other acute onset musculoskeletal features.

Of the eligible patients 37 had osteomyelitis (11 also had arthritis), 7 had septic arthritis without osteomyelitis, 19 had skin infection, 198 had non-infectious arthritis (109 transient, 40 JIA, 28 post-infectious, 20 vasculitis, 1 SLE) and 168 had other conditions.

We found a total annual incidence rate of osteomyelitis in children of 13 per 100 000. Thirty-five percent had subacute osteomyelitis. Osteomyelitis was most common in patients under 3 years of age. ESR was the best laboratory test for identifying osteomyelitis patients, but the highest positive predictive value was only 26%. The most frequent bone involvements were the long bones. Vertebral osteomyelitis was common (24%). Blood cultures were negative for all patients with subacute osteomyelitis and only positive for 26% of patients with acute osteomyelitis. The temperature and the laboratory test results were higher for patients with acute osteomyelitis than for patients with subacute osteomyelitis. In addition, subacute MRI signs were present in 69% of osteomyelitis patients with more than 14 days` disease duration.

## **Paper IV**

### **Predictors of Juvenile Idiopathic Arthritis in a population-based cohort of children with very early arthritis**

We wanted to assess the ability of patient characteristics, disease variables and laboratory variables to predict the diagnosis of juvenile idiopathic arthritis (JIA). The diagnostic outcomes of 214 patients were obtained by chart reviews after two years.

In the present study, predictors of the evolution of JIA in very early childhood arthritis were small-joint involvement, symptom duration for more than two weeks, a neutrophile WBC-

count in the normal range, knee-joint involvement and a platelet-count above the normal limit. The same determinants discriminate between JIA and transient/postinfectious arthritis. Determinants that discriminate JIA from infectious arthritis are the absence of fever and a low occurrence of hip-joint involvement.

# DISCUSSION

## Methods

### General aspects on study design

The strength of this study is that it is prospective and population-based. In Norway the majority of patients receive care in their county of residence, and the homogeneous health care and social security system based on equality of access facilitates recruitment to epidemiological studies <sup>144</sup>.

First a group of patients with possible arthritis and/or osteomyelitis was identified. On hospital admission physicians could rule out other diagnoses assisted by radiological methods. This was done to estimate the annual incidence and to obtain a representative cohort. Then the patients were followed for six months (and in some cases up to three years) and the cohort was subdivided into groups with different characteristics. This type of research design can be called an observational, prospective and longitudinal study design. This design is frequently used to investigate prognosis, the natural history of disease and to investigate possible associations between factors and a particular condition <sup>145</sup>.

We had a small number of patients with septic arthritis which made a meaningful statistical comparison with that group difficult. By only using hospital patient registries we would have had larger number of patients and we could have been able to follow incidence rates for many years, however the problem of correct ICD coding of patients, variation in laboratory and radiological assessments and selection of patients would have limited the interpretation of the results.

The impact of positive microbiological test in our arthritis patients is uncertain as we did not compare with healthy controls. In addition different laboratory test methods were used in the different hospitals. Based on our design we could not test whether patients with *S. pyogenes* infection were more likely to have arthritis.

### Selection of patients

An important question is whether we did identify all patients with recent onset arthritis and/or osteomyelitis. We believe that our recruitment criteria included the most common signs and symptoms. Maybe however, we ought to have added the term “back-pain” as this can be a symptom in older children with sacroiliitis, pelvic osteomyelitis and vertebral osteomyelitis. In addition the term “not cause by trauma” could have been unclear to some physicians. On one hand a trauma can precede and play an important role in the pathogenesis of osteomyelitis. In addition a child with knee arthritis could fall and the parents would first observe the swollen knee after the minor trauma. On the other hand we wanted to avoid including patients with larger injuries or fractures. Nevertheless, on admission we never excluded patients due to a history of trauma. Due to

our recruitment criteria we also might have missed patients with > 6 weeks disease duration. This criterion was set to support early referral of patients with musculoskeletal signs and symptoms.

A limitation of our design is that we do not know if all primary care physicians participated in the study. This is supported by the fact that some patients had seen several physicians before admission. In addition the incidence rate of arthritis was higher in the city of Oslo than in other counties (although the incidence of JIA was similar) which suggests that not all mild cases were referred from areas where the distance to hospitals was longer. It is also possible that some patients could have been seen at alternative facilities such as Chiropractors. However, we believe that most patients were admitted as we sent several letters to primary care physicians and because of easy access to free of charge hospital care. In very mild cases the parents might not have searched for any help.

We believe that our arthritis and osteomyelitis patients are representative for South-eastern Norway. Approximately 25% of Norwegian children live in the study area; however, there could be regional variations in Norway. Overall few patients with arthritis (15%) or osteomyelitis (0%) were identified by chart review and therefore we had a high success rate in identifying arthritis and osteomyelitis patients upon admission. In many cases patients who were identified retrospectively were also able to attend the planned follow-up visits.

### **Loss to follow-up**

We put a great effort in avoiding loss of follow-up. At six months the attendance rate was at 98-39%. Parents were repeatedly requested to attend the six weeks and six months visits and were offered new and flexible schedules if they were unable to attend the planned visits. Two patients moved out of our region. Our main impression was that loss of follow-up was due to lost interest as the patients had no further signs or symptoms.

### **Variety in examinations and treatment**

An important research problem was that not all patients were investigated equally closely. Patients who appeared ill or were believed to have a chronic disease had more tests, received treatment on an individual basis and also had additional follow-up. Due to our study design which included ethical aspects we did not suggest MRI and tissue cultures in all patients. Many of our patients were young and required general anaesthesia for such procedures. Nevertheless, we believe that the number of patients who received an MRI was high (127 patients). There were difficulties in performing blood tests and to receive enough blood from all patients. We prioritised blood tests which would have a direct impact on the treatment of the patients and this may explain why few patients were tested for e.g. HLA-B27. Patients who were not willing to have blood tests or radiological examinations were not excluded from our study.

## Inter-rater reliability

In order to identify arthritis patients with rapid remission many children were first seen by the paediatrician or rheumatologist on call. Inter-rater reliability for the assessment was not tested and variability between the observers may have influenced our results, especially in patients with early remission.

## Classification of the patients

We classified patients with JIA according to the ILAR criteria and patients with Acute Rheumatic fever (ARF) according to the revised Jones criteria. There are no established classification criteria for osteomyelitis or for other subgroups of arthritis. According to the ILAR criteria, the arthritis must persist for at least six weeks with exclusion of other well defined diseases; however there are reports that patients with enteropathic arthritis or PSRA may have a disease duration of more than six weeks <sup>23, 46</sup>. When can a patient with persistent arthritis who test positive for microbes be classified as JIA? Could this be done after six weeks, six months, two years or ever? The role of S. pyogenes in patients with JIA remains uncertain. <sup>146</sup>

## Results

### Incidence

We found a total annual incidence rate of childhood arthritis of 71 per 100 000 and of osteomyelitis of 13 per 100 000. A higher incidence of arthritis, 109 per 100 000, was found in a similar study of Urban Finnish children by Kunnamo *et al* (1986) <sup>3, 7, 8</sup> (table 4). A comparison between Kunnamos and our study (paper I) is shown in table 5.

**Table 4. Annual incidence of recent-onset arthritis in children in population-based studies**

Author (ref)	Location	Method	n	Incidence 100 000/yr	Incidence of different types of arthritis 100 000/yr			Post- infectious	Proportion JIA/JCA
					JIA/JRA	Transient	Septic		
Riise <i>et al</i> , 2008 (1)	Norway <sup>1</sup>	Clinical	182	71	14	43	3	9	20%
Kunnamo <i>et al</i> , 1986 (3)	Finland <sup>2</sup>	Clinical	161	109	19	78	7	5 <sup>3</sup>	17%
Von Koskull <i>et al</i> , 2001 (7)	Germany <sup>4</sup>	Questionnaire	319	83	7	76	NA	NA	8%
Savolainen <i>et al</i> , 2003 (8)	Finland <sup>5</sup>	clinical	11	64	23	23	NA	17 <sup>6</sup>	36%

<sup>1</sup> Oslo, Akershus and Buskerud; <sup>2</sup> Helsinki; <sup>3</sup> Enteropathic; <sup>4</sup> Bavaria, cities; <sup>5</sup> Kuopio; <sup>6</sup> Sindbis virus  
NA = not assessed

**Table 5. Comparison of studies on the incidence of childhood arthritis**

	Riise <i>et al</i> , 2008 (1)	Kunnamo <i>et al</i> , 1986 (3)
Number of patients	182	161
Age, median, years	4.9	NA
Female, %	38	42
Recruitment period	June 1, 2004-May 31 2005	May 1, 1982- April 30, 1983
Recruitment area	Eastern Norway, 1/3 urban, 2/3 commuter/rural	Grater Helsinki, urban
Referral criteria	1) Joint swelling or 2) Limited range of motion in ≥ 1 joint or walking with a limp or other functional limitations affecting arms and/or legs or 3) Pain in ≥ 1 joint or extremity together with elevated CRP, ESR or WBC	Swelling or limitation of motion of a joint or walking with a limp or hip pain
Definition of arthritis	1) Swelling of a joint 2) Restricted mobility of a joint with warmth and/or tenderness and/or pain 3) Arthritis demonstrated by ultrasound or MRI	1) Swelling of a joint or 2) Limitation of motion with heat, pain or tenderness
Follow-up	6 weeks, 6 months, additional follow-up data 9-21 months	2 weeks, 3 months, additional follow-up data minimum 24 months
Microbiological studies	Yersinia, Borrelia, EBV, CMV, Chlamydia, mycoplasma, parvovirus B19, Hepatitis B, ASO, antiDNAseB, throat streptococcal smear, bacterial culture of feces, adeno and rota from feces	Yersinia, Salmonella, Campylobacter, Mycolpasma, Chlamydia, Toxoplasma, rubella, EBV, ASO, antistreptodornase, throat streptococcal smear, virus isolation from feces, parasite examination of feces
Duration of symptoms before inclusion	3 days, median	71% seen within one week
Annual incidence per 100 000	71; (88 Oslo, 70 Akershus, 44 Buskerud)	109
-Chronic arthritis, (%)	14 (20)	19 (17)
-Septic arthritis, (%)	3 (4) <sup>1</sup>	7 (6) <sup>2</sup>
-Post infectious, (%)	9 (13)	5 (5) <sup>3</sup>
-Transient, (%)	43 (60)	78 (71)
Viral arthritis	4 CMV, 3 rotavirus, 2 EBV, 1 mycoplasma, 1 varicella	1 measles, 1 varicella, 1 adenovirus

<sup>1</sup> 1 *S.aureus*, 1 *Kingella kingae*, 1 *S. pyogenes*, 1 GBS, 1 *S. pneumoniae* (3 microbes not identified); <sup>2</sup> 5 *S. aureus*, 5 *Hemophilus Influenzae*;

<sup>3</sup> enteropathic

In contrast to Kunnamo we did not ask for patients with hip pain as the only symptom, we included non-urban patients who had a lower incidence of arthritis compared to urban patients and we had less septic arthritis than in Kunnamo's study which is probably linked to the introduction of vaccination against *Haemophilus Influenzae*. We did not have any patient with *Yersinia enterocolitica* arthritis. *Yersinia* arthritis has been reported in several Finnish studies and both genetic and environmental differences could explain this finding <sup>57</sup>.

Our incidence of JIA at 14 per 100 000 was similar to other Nordic studies, although the incidence has been reported higher (19-23 per 100 000) in Northern- and Middle Norway and in Finland <sup>3, 7, 14-18, 147-151</sup> (table 6).

**Table 6. Incidence of chronic arthritis in European children**

Author (ref)	Method	Location	Term	Annual incidence/ 100 000
<i>Nordic countries</i>				
Moe et al, 1998 (15)	Hospital, retrospective	Norway, north	JCA <sup>1</sup>	23
Berntson et al, 2003 (14)	Population, prospective	Norway, north	JIA <sup>2</sup>	19
Riise et al, 2008 (I)	Population, prospective	Norway middle	JIA <sup>3</sup>	23
		Norway, east		14
Gare et al, 1992 (16)	Population, prospective	Sweden, west	JCA <sup>1</sup>	11
Berntson et al, 2003 (14)	Population, prospective	Sweden	JIA <sup>2</sup>	15
		Denmark, east		9
		Denmark, Århus		16
Kunnamo et al, 1986 (3)	Population, prospective	Finland, Helsinki	JRA	19
Kaipainen et al, 1996 (147)	Register, prospective	Finland	JRA	14
Kaipainen et al, 2001 (149)	Register, prospective	Finland	JRA	20
Berntson et al, 2003 (14)	Population, prospective	Finland, Helsinki	JIA	21
Östergaard et al, 1998 (148)	General clinics, retrospective	Denmark	JRA	6-8
<i>Other countries</i>				
Pruunsild et al, 2007 (150)	Population, prospective	Estonia	JIA	22
von Koskull et al, 2001 (7)	Population, prospective, questionnaire	Germany, south	JCA	6.6
Kiessling et al, 1998 (18)	Hospital, retrospective	Germany, Berlin	JCA <sup>4</sup>	3.5
Symmons et al, 1996 (151)	Register, prospective	UK, Liverpool	JCA	10
Prieur et al, 1987 (17)	Practitioner survey, retrospective	France	JCA	1.3-1.9

<sup>1</sup> arthritis not defined; <sup>2</sup> warm and painful joint(s) included in definition of arthritis; <sup>3</sup> arthritis= swelling of a joint or restricted mobility of a joint with warmth and/or tenderness and/or pain; <sup>4</sup> not SpA, PsA or IBD

A similar incidence rate of osteomyelitis was found in Tromsø, Northern Norway, at 10 per 100 000 (1965-1994) and in Lithuania at 11-14 per 100 000 (1982-2003). The significant reduction in Scotland over the past 30 years is probably due to methodology<sup>94, 100-104, 152</sup> (table 7). More large prospective studies with homogenous assessments and classification criteria are necessary to conclude whether there are true changes in the incidence of arthritis and osteomyelitis over time or between geographical areas.

**Table 7. Incidence of osteomyelitis in children**

Author (ref)	Method	Location	Period	Annual incidence 100 000/yr
Riise et al, 2008 (III)	Prospective, population	Norway, east	2004-05	13 (8 acute; 5 subacute)
Dahl et al, 1998 (102)	Retrospective, hospital	Norway, north	1965-94	8-12 (7% vertebral)
Craigen et al, 1992 (94)	Retrospective, hospital	Scotland	1970-90	9-4
Blyth et al, 2001 (103)	Retrospective, hospital <sup>1</sup>	Scotland	1990-97	7-3 ( 5-2 acute; 3 subacute)
Malcius et al, 2005 (152)	Retrospective, hospital <sup>2</sup>	Lithuania	1982-03	12-14 (acute)
Gillespie et al, 1979 (104)	Retrospective, register	New Zealand	1978-82	10 (European) 74 (Maori)
Krogsgaard et al, 1998 (100)	Retrospective, national register	Denmark	1991-93	0.4 (only vertebral, aged 0-9 yr)
Grammatico et al, 2007 (101)	Retrospective, national register	France	2002-03	0.3 (only vertebral, aged 0-20 yr)

<sup>1</sup> spine and skull excluded; <sup>2</sup> local pain and fever mandatory



In our study septic arthritis and osteomyelitis was most frequent in children < 3 years of age and in line with others the age distribution of JIA tends to be bimodal with higher incidence rates in children aged 1-3 years and in children aged 9-15 years<sup>14, 16, 21</sup>. Hence, patients < 3 years of age should be examined for these diseases.

## **Bones and joints**

In our study knee joint arthritis was as common as hip joint arthritis followed by ankle joint arthritis. However, very high numbers of patients with transient synovitis of the hip have been reported in the literature<sup>3, 7, 70, 71</sup>.

The finding of a low proportion of long bone involvement in our (paper III) and newer studies was different from older studies and a study from South Africa<sup>93, 99, 102, 112, 153, 154</sup>. This could be linked to improved standards of living and hygiene.

In line with other studies we found osteomyelitis to be most frequent in the lower extremities. On the other hand we found a high proportion of patients with vertebral osteomyelitis (24%) compared to most previous studies<sup>93, 99-101</sup>. Such cases have also been diagnosed as spondylarthritis, spondylodiscitis or discitis and there are no verified classification criteria on how to distinguish vertebral osteomyelitis from discitis<sup>102, 106, 155</sup>. Regardless of the use of terminology antibiotic treatment is recommended by most authors<sup>106, 110</sup>.

## **Microbiology**

Microbiological findings were present in 27% of our arthritis patients and among patients classified to all diagnostic groups. In a Swedish population based study of adults, 45% had signs or a history of recent infection. We found elevated streptococcal antibodies to be the most frequent finding. The percentage of positive streptococcal tests was low in very young children and peaked at patients aged 8-11 years (35%). Studies have found that the age-related incidence of ARF follows that of GAS pharyngitis and peaks between the ages of 6-15 years<sup>156, 157</sup>.

Viral antibodies for recent infection were positive in < 5% of our patients. The role of viruses in arthritis patients needs further study. However, in line with Kunnamo *et al*, we believe that viral antibody screening is of limited use for the clinician<sup>23</sup>.

Positive bacterial cultures in the osteomyelitis patients were present in 43% of the patients; only 26% of the acute osteomyelitis patients had a positive blood culture and no patient with subacute osteomyelitis had a positive blood culture. We and others found *S. aureus* to be the most common microbe<sup>93, 94</sup>. A high proportion of positive blood cultures have been found in previous studies of acute osteomyelitis patients. Hence, the use of tissue cultures is probably more important now than was the case in earlier studies.

## Predictors of JIA

We found that transient arthritis was three times more frequent than JIA followed by post-infectious arthritis which mainly comprised patients with PSRA.

The following predictors were associated with JIA : female gender, absence of mono arthritis and hip joint arthritis, the presence of knee joint arthritis, small joint arthritis, symptom duration of more than two weeks, normal neutrophile count, high platelet count, ANA, anti-CCP, IgM RF and HLA-B27.

Predictors for JIA in undifferentiated arthritis patients have previously only been studied by Kunnamo *et al* <sup>23</sup>. In patients with disease duration of more than two weeks, a low CRP value, the absence of fever and an elevated IgG were independent factors for chronic arthritis. A study from the UK showed that 94% of patients with more than two weeks disease duration had JIA <sup>158</sup>.

In line with other studies, immunological antibodies and HLA-B27 had a low sensitivity for JIA <sup>3, 14, 116, 150, 159</sup>. As ANA screening only was positive in one of our arthritis patient without JIA the problem of false positive tests seems minor in children. That ANA positivity is one of the most important risk factors for iridocyclitis is accepted <sup>159, 160</sup>. The HLA-B27 antigen is probably more common in the population in the northern parts of the Nordic countries than in the southern parts, ranging from 8 to 16% <sup>161, 162</sup>. A recent Nordic study reported that HLA-B27 predicted a more extended disease in older boys with JIA <sup>163</sup>.

We found a lower proportion of mono arthritis (64%) in JIA patients than in other types of arthritis. Polyarthritis have also found in 28% to 47% of children with post-infectious and para-infectious arthritis, but they normally have a short disease duration <sup>4, 23, 64, 164</sup>. Hence, we believe that involvement of more than four joints in patients with arthritis persisting for more than a few days may be associated with JIA.

The finding of knee joint arthritis as an independent predictor for JIA must be interpreted carefully as we and others have found knee joint arthritis in several patients with post-infectious, infectious or transient arthritis (29-41%) <sup>80, 165</sup>.

However, small joint arthritis is probably an important factor as it was rarely found in patients without JIA in our study and has been found in several patients with JIA in other studies <sup>5, 22, 165</sup>.

A normal neutrophile count as a marker for the differentiation of JIA versus other groups of arthritis has as far as we know not been investigated earlier and warrants further study. The fact that JIA patients had a longer duration of symptoms before admission than patients with other types of arthritis could explain that this acute phase reactant was lower than in the other subgroups.

A high platelet count predicted JIA in our study. Liang *et al* found higher levels of platelets in JIA than in reactive arthritis patients <sup>165</sup>. An elevated level of platelets is a finding in many patients with chronic inflammation <sup>166</sup>.

## PSRA

We found that patients with PSRA had a longer disease duration than patients with transient arthritis, this is in line with a previous study by Ahmed et al who found a mean duration of arthritis in PSRA patients of more than two months<sup>46</sup>. We also found that the duration of symptoms before admission was shorter, hip arthritis was more frequent, and knee/ankle arthritis or other joint involvement, positive ANA and HLA-B27, and persistent arthritis were less frequent in the PSRA than in the JIA patients. A review also found that HLA-B27 is rare in PSRA patients<sup>164</sup>. Although we used the proposed criteria for PSRA by Ayoub and Ahmed, it remains uncertain whether PSRA is a specific disease entity or if it is a heterogeneous group of diseases in which some patients ought to be classified with JIA or transient arthritis<sup>42, 164</sup>.

We believe that school-aged patients with recent onset arthritis should be tested for the presence of *S. pyogenes* as it is essential for the diagnosis of acute rheumatic fever and PSRA. In addition positive *S. pyogenes* tests assist in evaluating patients with disease duration of more than six weeks. Although our sample is small we do not have evidence that PSRA patients in Norway have a risk for carditis. A recently published retrospective Israeli study did not show carditis in any of the 159 PSRA patients examined<sup>167</sup>. The subject of PSRA, carditis and duration of penicillin prophylaxis is controversial<sup>47-49, 142, 164, 168, 169</sup>. Large population-based studies are needed to identify arthritis patients who need cardiological follow-up and treatment. Randomised-controlled trials should be assessed to find whether penicillin or penicillin prophylaxis can prevent carditis in children with PSRA.

## Characteristics of osteomyelitis

We found that osteomyelitis patients and especially subacute osteomyelitis patients had few clinical and laboratory signs of inflammation. This is in contrast to several earlier studies on acute osteomyelitis, but could be linked to selection of patients<sup>93, 102</sup>.

ESR was the laboratory test with the highest positive predictive value in our study. The high sensitivity of ESR is in line with most previous studies<sup>99, 113, 170</sup>. However, CRP has been found to be more sensitive in microbiologically confirmed acute osteomyelitis and reflected recovery better than ESR and WBC<sup>113</sup>.

We also demonstrated that ESR was higher in osteomyelitis patients with a disease duration of <14 days than ≥14 days. This could indicate that a decrease in ESR in untreated patients can not exclude osteomyelitis in patients with persistent musculoskeletal signs and/or symptoms. On the other hand, patients who are admitted with a negative ESR and duration of symptoms of less than two weeks have a minimal risk of osteomyelitis.

## MRI

In our study MRI had a sensitivity of 100% and a positive predictive value of 85% for identifying osteomyelitis patients. In the literature the high sensitivity of MRI is based on adult patient series (mainly on diabetic foot) and a few paediatrics series. Some of the studies of non-diabetic patients are shown in table 8<sup>125, 127, 129-132, 171, 172</sup>. We believe that based on MRI only, a poor defined bone marrow edema as a sign of osteomyelitis can be difficult or impossible to separate from bone edema in arthritis patients. Bone marrow edema has been found as a possible predictor of erosive progression in adult rheumatoid arthritis<sup>173</sup>.

**Table 8. Sensitivity and specificity of MRI in the diagnosis of osteomyelitis\***

Author (ref)	No. patients OM/not OM	Technique	Sensitivity	Specificity	Compared to	Location	Age, yr	Evaluation
Unger <i>et al</i> , 1987 (125)	12/23	T1W, T2W, PDV, GRE, STIR	92	96	Histology or follow-up	Mixed	1-80	Blinded, 2 observers
Erdman <i>et al</i> , 1991 (127)	54/56	T1W, T2W, PDV, STIR	98	75 <sup>1</sup> , 82 <sup>2</sup>	Histology or culture	Mixed	0-74	Limited clinical info, 3 observers
Zynamon <i>et al</i> , 1991 (171)	44/17	T1W, T2W, PDV, GRE	100	78	Histology or culture or follow-up	Mixed	1-83	Unknown
Morrison <i>et al</i> , 1993 <sup>1</sup> (132)	34/15	T1W with and without Fat-sat, T2W, i.v. gadopentetate dimeglumine	88	93	Histology or culture or follow-up	Mixed	10-80	Blinded, 2 observers
Mazur <i>et al</i> , 1995 <sup>1</sup> (131)	21/22	T1W, T2	97	92	Histology or follow-up	Mixed	0-15	Open, 1 observer
Huang <i>et al</i> , 1998 (172)	44(57 MRIs)	T1W, T2W, (STIR)	98	89	Histology or culture or follow-up	Pelvis, hip	22-83	Blinded
Riise <i>et al</i> , 2008 <sup>1</sup> (III)	35/92	T1W, STIR, (i.v contrast)	100	93	Histology or culture or follow-up	Mixed	0-15	Blinded, 2 observers

\* Studies of diabetic foot, small studies or studies of poor quality are not presented; <sup>1</sup> prospective; <sup>2</sup> retrospective OM= osteomyelitis, T1W=T1-weighted, T2W=T2-weighted, PDW= proton-density weighted, GRE=gradient-recalled echo, STIR=short tau inversion recovery sequence, Fat-sat= fat saturation

The MRI characteristics of acute osteomyelitis are ill defined bone marrow edema. In our study patients with disease duration of more than two weeks, 2/3 had sign of a subacute process. In a study by Erdman *et al*. 93% of the patients with more than four weeks disease duration had MRI signs of a subacute process<sup>127</sup>. The sign of a subacute process is probably linked to time, bone involvement, age of the child, virulence of the bacteria, host factors and MRI techniques.

We found that 31% of the osteomyelitis patients had increased signal and or thick synovia on MRI which could be interpreted as arthritis (paper III). This is in line with a study by Perlman *et al*<sup>174</sup>. This could support that all patients with monoarthritis of more than two weeks duration should be tested by MRI.

By ordinary MRI, due to time and cost, only a limited part of the body can be examined. Whole-body MRI (WBMRI) is a new technique that could be of use in patients with possible osteomyelitis where the location is unknown or multiple <sup>175</sup>.

A systematic review of adult chronic osteomyelitis patients found that fluorodeoxyglucose positron emission tomography (PET) had a higher diagnostic accuracy for the diagnosis than MRI <sup>176</sup>. The impact of PET scan in childhood osteomyelitis warrants further study.

### **Early arthritis and osteomyelitis in a public health perspective**

Although patients with possible arthritis/and or osteomyelitis are frequently seen in paediatric wards primary care physicians have little experience with such cases. We therefore suggest that a child who appears well should be referred to a hospital within few days. Based on our findings and the literature we can predict the risk for severe and/or chronic disease in many patients <sup>23, 69, 177</sup>.

Based on reports from low-income countries we know that untreated cases of septic arthritis, osteomyelitis and ARF could cause considerable morbidity and some mortality <sup>37, 178 179</sup>.

Due to new and possible efficacious treatments for JIA it is believed that early intervention can limit joint destruction, growth-disturbances, osteoporosis and reduced quality of life <sup>180-182</sup>. We are not aware of studies of health status and working ability in adults who had acute-, subacute- or chronic osteomyelitis in childhood.

Based on the epidemic in low-income countries, an economic analysis of ARF and rheumatic heart disease estimated that secondary prophylaxis was more effective than primary prophylaxis (US\$142 per DALY [disability adjusted life years] gained and \$5520 per death averted versus \$1049 per DALY gained and \$40920 per death averted) <sup>183</sup>. Primary prophylaxis is also probably of limited value because one study found that less than 20% of patients with ARF had throat symptoms that made them seek medical attention <sup>184</sup>. An effective vaccine against *S. pyogenes* could be available within some years. However, large subsidies are essential to give such a vaccine to the populations in need <sup>185</sup>.

In high income countries young children require general anaesthesia for tissue cultures and MRIs. In-patient-care increases the costs, the risk of medical care complications and may also involve some children with spontaneous remission of signs and symptoms.

From a public health perspective more research including cost-benefit analyses are needed to answer questions about identification of arthritis and osteomyelitis patients and the impact of early diagnosis and treatment. New diagnostic tools and treatment options continue to challenge a publicly financed health care system.

## CONCLUSIONS

- Arthritis is common in children, occurring in at least 0.7/1000 children per year. Twenty % of children presenting with early onset arthritis had JIA in the present study. The proportion and distribution of patients with septic, and post-infectious and transient arthritis was different from that reported in Finland 20 years ago. Geographical or genetical differences as well as environmental changes over time may influence the occurrence of childhood arthritis (paper I).
- Septic arthritis and osteomyelitis were most common in patients under three years of age. The incidence rate in JIA tends to be bimodal with slightly higher incidence rates in the age group 1 to 3 years and in school aged children. Hence patients < 3 years of age should be examined for septic arthritis, osteomyelitis and JIA (paper I, III).
- Hip involvement is associated with transient arthritis, while hip arthritis rarely is the presenting symptom in JIA. Female gender, extended joint involvement, knee joint arthritis, small joint involvement, symptom duration > 2 weeks, high platelet count, neutrophile WBC-count in normal range, ANA, anti-CCP and HLA-B27 correlates with JIA (paper I, IV)
- Signs of a recent or current infection were found in ¼ of the arthritis patients and in all subgroups. A viral antibody screen was of little clinical value (paper I).
- The presence of *S.pyogens* is common in school aged children and can predict a prolonged disease course, but did not predict carditis in this small group of patients with arthritis associated to *S. pyogenes* (paper I, II).
- The incidence of osteomyelitis in Norway remains high. Long bone involvement is probably less common than in earlier studies. Blood culture is insufficient to identify microbes in most cases (paper III).
- Vertebral osteomyelitis was present in one of four osteomyelitis patients in our study (paper III).
- MRI shows a high sensitivity and specificity for osteomyelitis. However, early signs are unspecific and must be compared with clinical history (paper III).
- Patients with subacute osteomyelitis have more defined MRI characteristics, but the acute phase reactants may be normal (paper III).

## **ERRATA**

In paper IV the correct address of Øystein R. Riise is “Department of Paediatrics, Ullevål University Hospital and Department of Rheumatology, Rikshospitalet Medical Centre”

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## **APPENDIX: Papers I – IV**





## Research article

## Open Access

# Childhood osteomyelitis-incidence and differentiation from other acute onset musculoskeletal features in a population-based study

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## Abstract

**Background:** Osteomyelitis can be difficult to diagnose and there has previously not been a prospective approach to identify all children in a defined geographic area. The aim of this study was to assess the annual incidence of osteomyelitis in children, describe the patient and disease characteristics in those with acute (< 14 days disease duration) and subacute osteomyelitis (≥ 14 days disease duration), and differentiate osteomyelitis patients from those with other acute onset musculoskeletal features.

**Methods:** In a population-based Norwegian study physicians were asked to refer all children with suspected osteomyelitis. Children with osteomyelitis received follow-up at six weeks, six months and thereafter as long as clinically needed.

**Results:** The total annual incidence rate of osteomyelitis was 13 per 100 000 (acute osteomyelitis 8 and subacute osteomyelitis 5 per 100 000). The incidence was higher in patients under the age of 3 than in older children (OR 2.9, 95% CI 2.3–3.7). The incidence of non-vertebral osteomyelitis was higher than the incidence of vertebral osteomyelitis (10 vs. 3 per 100 000;  $p = .002$ ). Vertebral osteomyelitis was more frequent in girls than in boys (OR 7.0, 95% CI 3.3–14.7). ESR ≥ 40 mm/hr had the highest positive predictive laboratory value to identify osteomyelitis patients at 26% and MRI had a positive predictive value of 85%. Long-bone infection was found in 16 (43%) patients. ESR, CRP, white blood cell count, neutrophils and platelet count were higher for patients with acute osteomyelitis than for patients with subacute osteomyelitis. Subacute findings on MRI and doctor's delay were more common in subacute osteomyelitis than in acute osteomyelitis patients. Blood culture was positive in 26% of the acute osteomyelitis patients and was negative in all the subacute osteomyelitis patients.

**Conclusion:** The annual incidence of osteomyelitis in Norway remains high. ESR values and MRI scan may help to identify osteomyelitis patients and differentiate acute and subacute osteomyelitis.

## Background

Haematogenous osteomyelitis is an inflammation of bone and bone marrow, usually caused by bacterial infections, but occasionally caused by fungi, viruses or parasites.[1] Osteomyelitis may cause growth changes or pathological fractures.[2,3]

Acute haematogenous osteomyelitis is usually defined as a history of relevant signs or symptoms of less than 14 days, and subacute haematogenous osteomyelitis as a history of such signs or symptoms of more than 14 days.[4,5] Chronic osteomyelitis evolves over months or years and is characterized by dead bone (sequestrum) and fistulous tracts.[6]

Patients with bone abscesses may have a normal leukocyte count and erythrocyte sedimentation rate (ESR), which makes diagnosis difficult.[7] Bone destruction is not apparent on plain radiographic films until 7 to 10 days after infection.[8] Bone scans are sensitive in the diagnosis of osteomyelitis (73% to 100%), [9-11] but the difficulty in separating bone-marrow processes from soft-tissue disease limits specificity and accuracy.[12] Sensitivity of MRI in the diagnosis of osteomyelitis in adults and children is reported at 88% to 100%, with specificity of 75% to 100%. [12-17]

Studies from Scotland have shown a decline in incidence from 8.7 per 100.000 in 1970 to 2.9 per 100 000 in 1997. The clinical presentation changed from acute to subacute osteomyelitis, and there was a decline in long bone involvement.[3,18] However, a Lithuanian study has shown a rise in the incidence of osteomyelitis from 11.5 per 100 000 in 1982 to 14.3 in 2003.[19] The incidence of vertebral osteomyelitis in children has only been reported from National Patient Registries at < .5 per 100 000.[20,21]

To our knowledge, the incidence of osteomyelitis in children has previously only been reported in retrospective studies and patients with osteomyelitis have only been compared to patients with other acute onset musculoskeletal features in small scale pediatric studies.[14,22] Nor are we aware of any population-based comparative description of patients with acute and subacute osteomyelitis.

We aimed to determine the annual incidence rate of osteomyelitis in children and compare the patient and laboratory characteristics of osteomyelitis patients with those of patients who had other acute onset musculoskeletal features. In addition, we wanted to compare the age, sex, doctor's delay, clinical and MRI characteristics of children with acute and subacute osteomyelitis.

## Methods

### Background population

We conducted a population-based multi-centre study in three counties in South-Eastern Norway (Akershus, Buskerud and Oslo) between May 1, 2004 and June 30, 2005. The total number of children under the age of 16 was 255 303 on January 1, 2004.[23] In Norway the majority of patients receive care in their county of residence, and the homogeneous health care and social security system based on equality of access facilitates recruitment to epidemiological studies.[24]

### Recruitment

The children were examined at county pediatric departments or at the regional department of rheumatology (i.e. at Akershus University Hospital, Buskerud Hospital, Ullevål University Hospital, or Rikshospitalet Medical Centre). All primary care physicians were sent a letter every three months asking them to refer children with possible or evident osteomyelitis or arthritis to the appropriate hospital on the day the patient was first seen. The recruitment criteria were one or more of the following characteristics (under six weeks' duration and not caused by trauma): 1. joint swelling; 2. limited range of motion of one or more joints, walking with a limp or other functional limitations affecting arms and/or legs; 3. pain in one or more joints or extremities together with CRP > 20 mg/L and/or ESR > 20 mm/hr and/or WBC >  $12 \times 10^9/L$ . [25]

At the end of the study, we searched the hospitals' computerized records for 181 relevant diagnoses [based on the International Classification of Diseases, 10th edition (ICD 10) [26]] to identify any patients who met the recruitment criteria but had not been included.

### Inclusion criteria

Only patients younger than 16 who were permanently resident in the participating counties were included. The diagnosis of osteomyelitis was based on the characteristic signs and symptoms of bone infection and one of the following: 1. Positive culture from bone biopsy and/or histology showing inflammation; 2. MRI findings consistent with osteomyelitis; and 3. Positive bone scan if bone biopsy and/or MRI were not done.

### Exclusion criteria

Patients without laboratory examinations and patients who had chronic recurrent multifocal osteomyelitis, sickle cell anemia, fractures or malignant disease were excluded.

### Classification procedure

Follow-up data from medical charts relevant to the final diagnosis were included up to May 2007 (range 22–36 months). Two researchers recorded the clinical informa-



tion independently on a standardized form. In cases of disagreement, the classification was established in consultation with specialists in pediatric infectious diseases and pediatric rheumatology. Written informed consent was obtained from the parents of the children included in the study. The Regional Ethics Committee for Medical Research and the Ombudsman for Privacy in Research at the Norwegian Social Science Data Services approved the study.

### **Classification criteria**

Acute osteomyelitis was defined as a history of relevant symptoms of less than 14 days and subacute osteomyelitis as a history of symptoms of 14 days or more.

Arthritis was defined as inflammation of the synovia.[27] Septic arthritis was defined as bacteria cultured from synovial fluid and/or synovial fluid with WBC count  $> 50 \times 10^9/L$ .

### **Clinical and laboratory assessments**

Laboratory, microbiological and radiological tests were performed at each of the hospitals as part of the routine diagnostic procedure. Hemoglobin, WBC with differential, CRP (quantitative turbidimetric or immunoturbidimetric method) and ESR (conventional Westergren method) were assessed on admission. Clinical follow-up was planned for six weeks and six months after admission.

### **Radiological tests**

Three-phase bone scan ( $^{99m}Tc$  methylene diphosphonate) was recommended if there was doubt about the localization of the osteomyelitis. MRI was recommended within 3 days if mono- or oligoarthritis of  $< 2$  weeks' duration occurred in combination with one of the following four: 1. fever  $> 38.5^\circ C$ ; 2. CRP  $> 30$  mg/L or ESR  $> 30$  mm/hr or WBC  $> 12 \times 10^9/L$ ; 3. excessively painful joint or bone; 4. other suspicious factors for osteomyelitis or septic arthritis. We also recommended that MRI should be performed within 14 days if arthritis persisted for more than one week in one to three joints.

Two experienced radiologists retrospectively evaluated the MRIs, blinded to all clinical information except for the patient's age and that there was clinical concern for osteomyelitis. In cases of bone marrow edema, subacute osteomyelitis was defined as well-circumscribed lesions with homogeneous or peripheral contrast enhancement, periosteal inflammation, fibrosis, fistula or sequester. Acute osteomyelitis was defined as a poor interface between the normal and diseased bone marrow. The radiologists also reported the presence of arthritis in a nearby joint, other soft tissue abnormalities, and other orthopedic conditions. The MRIs were performed in different machines in different hospitals (1.0 T or 1.5 T). The MRI examinations

had at least one T1 spin echo sequence and one STIR (Short T1 Inversion Recovery) sequence. In most cases (and in every case with well circumscribed lesions), there was also at least one contrast-enhanced T1 spin echo sequence.

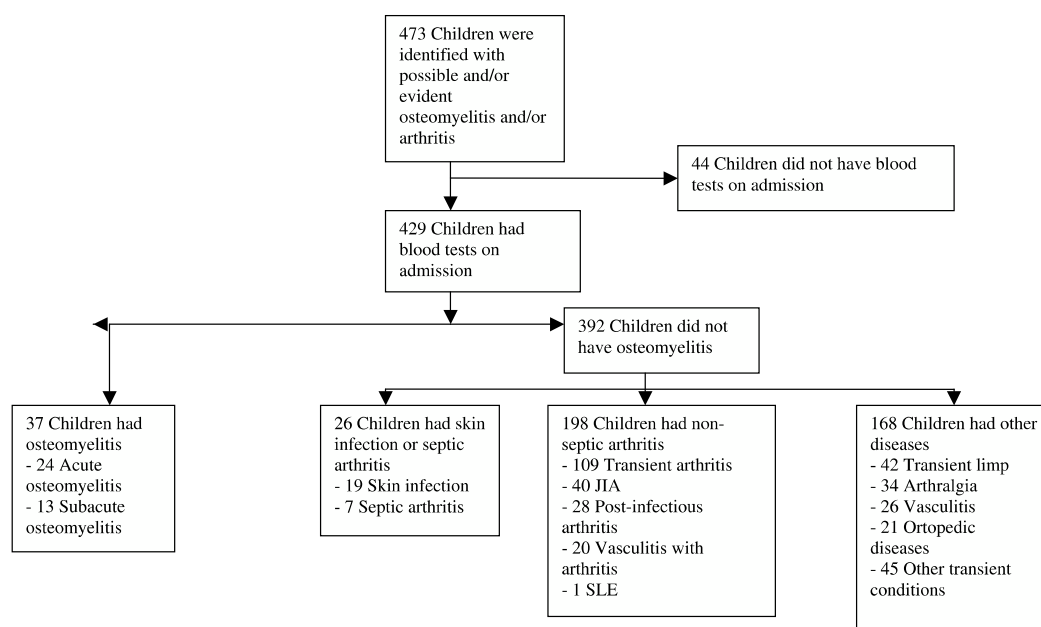
One of the radiologists was then informed of the final diagnosis, and evaluated the follow-up plane radiographs and/or MRIs of the osteomyelitis patients in order to report the presence of any remaining signs or sequelae.

### **Statistics**

Relations between categorical variables were studied using Chi-square test or Fisher's exact test. The continuous variables in our study were not normally distributed. Non-parametric tests were used: the Mann-Whitney-Wilcoxon test for comparison between two groups and the Kruskal-Wallis test for comparison between multiple groups. The continuous variables were described by reference to the median and interquartile range. The sensitivities and specificities of the laboratory tests used to discriminate between patients with and without osteomyelitis were presented graphically using ROC curves. The area under the ROC curve (ROC AUC) provides a measure of the overall discriminative ability of the test. AUC equals .5 when the ROC curve corresponds to random chance, and 1.0 when there is perfect accuracy.[28] P-values of  $< .05$  were considered significant, however, P-values of  $< .01$  were considered significant when we compared more than two groups (Additional file 1). All analyses were performed using SPSS for MS Windows, version 13.

### **Results**

Four hundred and twenty-nine (91%) of 473 patients recruited to our study underwent laboratory examinations and were considered eligible for further analysis (Figure 1). Thirty-seven patients had osteomyelitis, 26 had septic arthritis or a skin infection, 198 had non-infectious arthritis and 168 had other conditions. Two hundred and ninety-eight (69%) of the 429 patients were included prospectively, and 131 (31%) were identified by chart review. Thirty-six (97%) of the osteomyelitis patients and 234 (60%) of non-osteomyelitis patients received follow-up at six weeks, and 33 (89%) osteomyelitis patients and 151 (39%) non-osteomyelitis patients received follow-up at six months. The osteomyelitis patients who did not attend the planned follow-up reported (on their previous visit or by telephone) that they did not need further medical care. Non-osteomyelitis patients with persistent symptoms received further specialist health care. There was no difference as regards age, sex and duration of symptoms between the patients who fulfilled the inclusion criteria and had blood tests on admission, and those who were excluded or did not have blood tests (data not shown).

**Figure 1**

**Flow chart showing recruitment of children with osteomyelitis.** JIA- Juvenile Idiopathic Arthritis; SLE – Systemic Lupus Erythematosus.

### ***Incidence of osteomyelitis***

The annual incidence rate of osteomyelitis was 13 per 100 000 children under 16 years of age (Additional file 2). The incidence of non-vertebral osteomyelitis was higher than the incidence of vertebral osteomyelitis (10 vs. 3 per 100 000,  $p = .002$ ). The incidence of osteomyelitis was higher in patients under the age of 3 than in older children (OR 2.9, 95% CI 2.3–3.7). Vertebral osteomyelitis was more frequent in girls than in boys (OR 7.0, 95% CI 3.3–14.7).

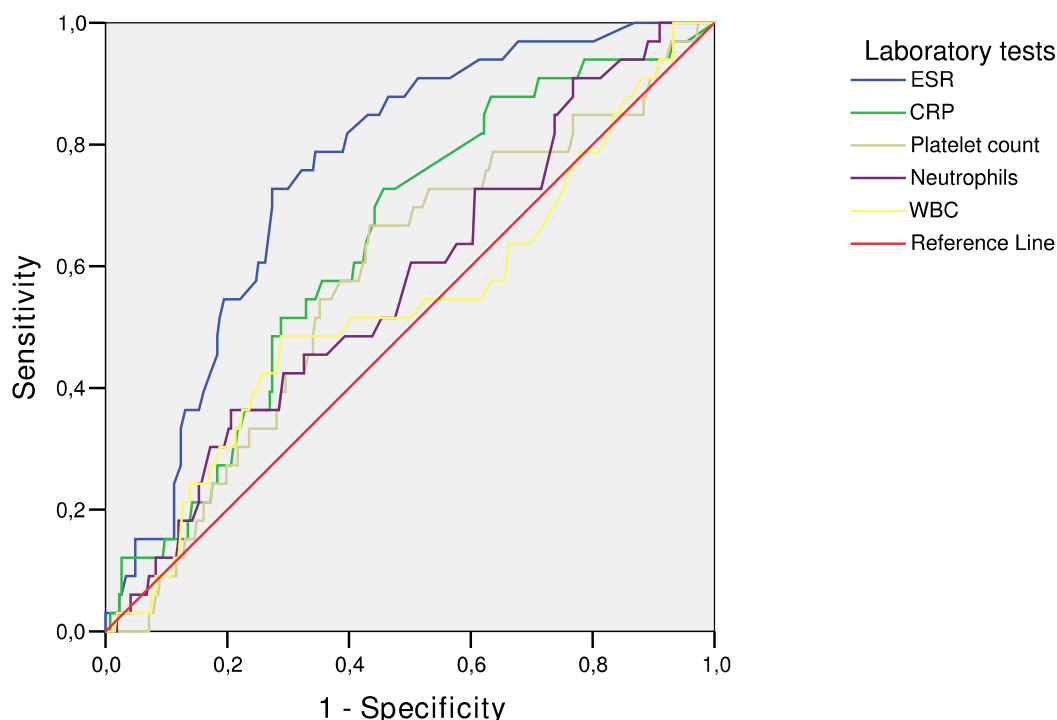
### ***Osteomyelitis patients versus children with other acute onset musculoskeletal features***

Figure 2 shows the ROC curves for ESR, CRP, WBC, neutrophils and platelet counts when used to discriminate between patients with and without osteomyelitis. ESR had the highest ROC AUC (.754; 95% CI .680–.828), followed by CRP (.638; 95% CI .545–.731).

Among the laboratory variables, ESR  $\geq 40$  mm/hr had the highest positive predictive value at 26% for identifying patients with osteomyelitis (Additional file 1). ESR  $< 20$  mm/hr had the lowest positive predictive value at 3%.

Nineteen (51%) of the 37 osteomyelitis patients were girls. The median age at presentation was 4.3 years (Additional file 3). In addition to clinical signs and symptoms the diagnosis of osteomyelitis was based on bone biopsy and MRI in 11 patients (2 had a negative culture but were positive on histology), on MRI alone in 24 patients and on bone scan alone in 2 patients (MRI and/or bone biopsy not assessed). One of the patients received corticosteroids due to adrenocortical insufficiency, and another child had C2 immunodeficiency.

Patients with osteomyelitis had a longer history of symptoms than patients with septic arthritis or skin infection or non-septic arthritis ( $p < .001$ ,  $p = .001$ ). The period between the first physician visit and the first hospital visit was longer for patients with osteomyelitis than for patients with septic arthritis or skin infection or non-septic arthritis ( $p < .001$ ,  $p = .001$ ). ESR and CRP were higher in patients with osteomyelitis than in patients with non-septic arthritis or patients with other conditions ( $p < .001$ ). The presenting symptom, clinical examination and bone involvement in the osteomyelitis patients are presented in Additional file 4.



**Figure 2**  
**ROC curves of laboratory tests used during the first visit to discriminate between patients with osteomyelitis (n = 37) and patients without osteomyelitis (n = 392).** The curves plot the relationship between the true positive rate (Sensitivity, y-axis) and the false positive rate (1 - Specificity, x-axis) at different cut-off titers. The higher the cut-off titer that is chosen, the lower the sensitivity and the higher the specificity, and visa versa. The diagonal reference line (area under curve (AUC) = .5), indicates no discrimination. The greater the distance of the curve from the diagonal, the higher the overall discriminative ability of the test.

### Radiological findings

Plain radiographs of the affected areas were assessed for 35 (95%) of 37 patients with osteomyelitis, and 251 (64%) of 392 non-osteomyelitis patients.

Bone scans showed bone uptake on the location of osteomyelitis in 13 (68%) of the 19 osteomyelitis patients tested, and showed bone uptake in 20 (53%) of the 38 non-osteomyelitis tested. This gave a sensitivity of 68%, specificity of 47%, a positive predictive value of 39% and a negative predictive value of 75%. The six patients with a false negative bone scan (4 total negative, 1 wrong location, 1 only soft tissue uptake) were younger than the patients with a true positive bone scan (age median 1.7, range 1.3–2.5 vs. median 9.2, range 1.1–13.9;  $p = .018$ ).

Bone marrow edema was found in 57 (45%) of 127 patients using MRI after retrospective evaluation. Bone marrow edema was present in all the 35 osteomyelitis patients who were tested. The MRIs could not exclude osteomyelitis in six (27%) of 22 patients who had bone marrow edema and other diagnosis: three had hand joint arthritis, one had knee joint arthritis, one had post-traumatic pain syndrome, and one had osteoid osteoma. This gave a sensitivity of 100%, specificity of 93%, a positive predictive value of 85% and a negative predictive value of 100%.

### Acute and subacute osteomyelitis

The age distribution of the 24 acute and the 13 subacute osteomyelitis patients is shown in Figure 3. The period between the first physician visit and admission to hospital

was longer for patients with subacute osteomyelitis than for patients with acute osteomyelitis ( $p < .001$ ) (Additional file 5). On admission, the median temperature, ESR, CRP, WBC and neutrophils were higher in patients with acute osteomyelitis than in patients with subacute osteomyelitis ( $p = .007$ ,  $p = .012$ ,  $p = .019$ ,  $p = .008$ ,  $p = .003$  respectively).

An MRI sign of subacute osteomyelitis was found in 9 (69%) of the patients with subacute osteomyelitis and in 6 (27%) of those with acute osteomyelitis ( $p = .013$ ).

There was no statistical difference between acute and subacute osteomyelitis patients as regards the presenting symptoms, clinical examination on admission or the anatomic location (data not shown).

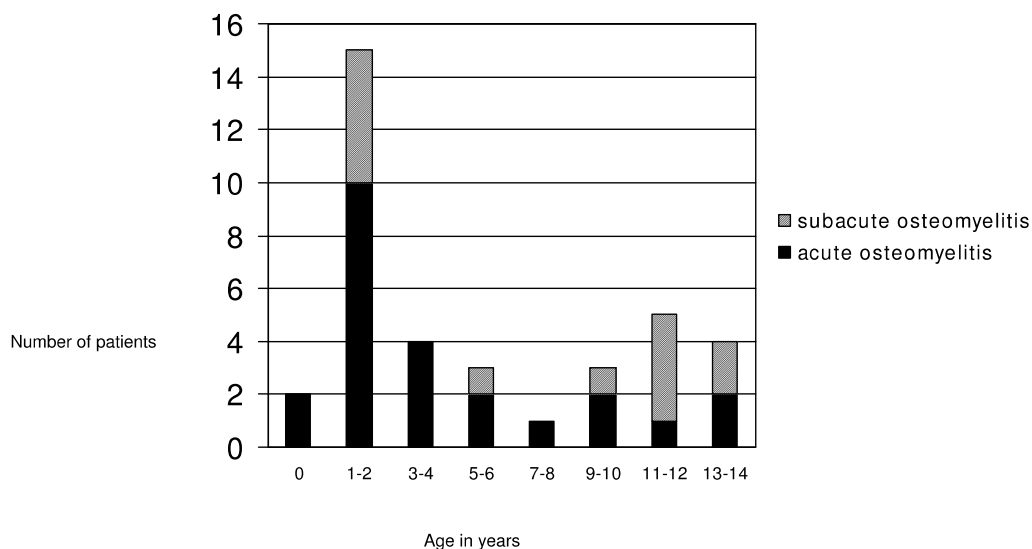
#### Treatment and outcome

Thirty-four (92%) of 37 osteomyelitis patients received antibiotics. In 33 (97%) patients, these were administered first intravenously and later orally. The median duration of treatment was 42 days (range 14–137) and the median duration of intravenous treatment was 14 days (range 12–49). Beta-lactamase-resistant penicillin, cloxacillin, was given intravenously to 28 patients (82%) of whom 12 received it in combination with ampicillin. Clindamycin

was administered orally to 23 (70%) of 33 patients. For eight patients (24%), the antimicrobials had to be changed due to rash. No patient had Methicillin-resistant *S. aureus*.

Six months after admission, none of the osteomyelitis patients had a history or clinical sign of an ongoing infectious bone process. Thirty-four patients (92%) had radiological follow-up [plain radiograph ( $n = 23$ ), MRI ( $n = 17$ ), at a median time of 3 months after admission (range 1 to 37)]. The MRIs revealed reduction or disappearance of bone marrow edema in all patients and sequestrum or fistula in two of the subacute osteomyelitis patients (3 months after admission). The most frequent findings in the nine vertebral osteomyelitis patients were decreased height of vertebral bodies ( $n = 8$ ), decreased disc space with endplate irregularities on both sides of the disc ( $n = 7$ ) and pathological angle of the vertebral axis ( $n = 4$ ). One of the two patients without disc inflammation developed a Schmorl's node. No patients had isolated discitis.

The three osteomyelitis patients who did not receive antimicrobials were identified after reevaluation of the MRIs. These patients recovered clinically within two months, but radiological follow-up showed erosion or sclerosis of the affected bones.



**Figure 3**  
**Age on admission of patients with acute osteomyelitis ( $n = 24$ ) and subacute osteomyelitis ( $n = 13$ ).**

## Discussion

This is the first study that aimed to identify all children with osteomyelitis in a defined geographic area. We found a total annual incidence rate of osteomyelitis in children of 13 per 100 000. Thirty-five percent had subacute osteomyelitis. Osteomyelitis was most common in patients under 3 years of age (28 per 100 000). ESR was the best laboratory test for identifying osteomyelitis patients, but the highest positive predictive value was only 26% (ESR  $\geq$  40 mm/hr). The most frequent bone involvements were the long bones. Vertebral osteomyelitis was common (24%). Blood cultures were negative for all patients with subacute osteomyelitis and only positive for 26% of patients with acute osteomyelitis. The temperature and the laboratory test results were higher for patients with acute osteomyelitis than for patients with subacute osteomyelitis. Subacute MRI signs were present in 69% of the osteomyelitis patients with disease duration of more than 14 days. The median doctor's delay was 63 days in the subacute osteomyelitis patients.

A limitation of this study is that, due to the recruitment criteria, children with disease duration of more than six weeks and children with trauma may not have been included. We wanted to avoid including children with larger injuries or fractures. However, on admission patients with a history of trauma were not excluded. There are studies indicating that a history of trauma can precede osteomyelitis.[2] As symptoms like back pain and refusal to sit were not among our recruitment criteria, we may not have identified all patients with vertebral osteomyelitis. Although all primary care physicians were repeatedly invited to participate in our study, we have no verification that our request was followed up in every case. In addition, few non-osteomyelitis patients underwent MRI and/or bone scans and/or had follow-up at six weeks and six months. However, the vast majority of patients who did not receive further diagnostic tests or follow-up either received a specific diagnosis or no longer showed symptoms after a few days. The clinical value of testing these patients would probably have been limited. A further limitation was that only 13 (35%) of 37 osteomyelitis patients underwent bone biopsies, which probably led to the low number of patients with a positive microbiological test. Twenty-four (65%) of the osteomyelitis patients were classified on the basis of clinical features and MRI. A poor interface between the normal and diseased bone marrow was found in acute osteomyelitis cases. This is known in the literature.[29] Sensitivity of MRI in the diagnosis of osteomyelitis in adults and children is reported at 88% to 100%, with a specificity of 75% to 100%. [12-17] Assets like fat suppression and contrast enhancement may not help to distinguish infectious from non-infectious inflammatory conditions on MRI.[15] As trauma, acute infarction in sickle cell anemia, recent radiation therapy,

osteoid osteoma and medullary tumors may all simulate the signal alterations seen with osteomyelitis, clinical and plain radiograph correlations are essential if MRI is being used for diagnostic purposes.[14,15,30] All of our osteomyelitis patients diagnosed using MRI had a clinical history and plain radiographs that supported the diagnosis.

Bone scans were false negative in six osteomyelitis patients under 3 years of age. Some reports have found a low sensitivity in the very young.[31,32] However, Aigner *et al* have shown that bone scans are highly sensitive in relation to very young children.[33] It is thought that bone scans are positive within the first week [34], and we may have assessed bone scans too early in the disease course. As not all patients were tested with bone scan our data should be interpreted cautiously.

Our total incidence of osteomyelitis at 13 per 100 000 was similar to retrospective studies in Norway and Lithuania (10 to 14 per 100 000).[19,35] The incidence in Maori children was very high at 74 per 100 000.[36] The low incidence in Scotland at 3 per 100 000 could be due to methodology.[18] We believe that a prospective methodology is an asset in identifying mild cases. Thirty-five percent of our patients had subacute osteomyelitis. In the Scottish studies, 50% of patients had subacute osteomyelitis, i.e. there was an increase in the proportion of children with subacute osteomyelitis and a decline in the total incidence of osteomyelitis in children of more than 50% between 1970 and 1997.[3,18] Long bones were affected in 43% of our patients. This was similar to newer series of patients at 33% to 51% [37-39], but lower than older series and a series from South Africa at 75% to 95%.[2,5,35] The development of a higher proportion of subacute osteomyelitis and a lower proportion of long bone involvement could be linked to improved standards of living and hygiene.

Twenty-four percent of our osteomyelitis patients had vertebral involvement (annual incidence of 3 per 100 000). In a retrospective series from the US, vertebral involvement was found in 19% of patients with subacute and chronic osteomyelitis, [37] although it was infrequent in most previous series.[2,20,21] Seven of our patients could have been defined as spondylodiscitis. As none of our patients had an isolated inflammation of the disc we considered the term "discitis" inappropriate in this context. Such cases have been variously diagnosed as osteomyelitis, spondylitis or discitis, and this makes a comparison difficult.[35] There are no verified classification criteria on how to distinguish discitis from vertebral osteomyelitis.[40]

Our osteomyelitis patients had a median age of 4.3 years, which is similar to that found in Scotland, [18] although

the patients in Latvia were older, at 10 years.[19] We found an equal distribution of osteomyelitis between the sexes, which was consistent with another Norwegian study.[35] However, in other countries osteomyelitis has been reported to be more frequent in boys.[2,19]

We found that ESR was the best laboratory test for identifying osteomyelitis patients. It was elevated in 83% of patients on hospital admission, and had a median value of 41 mm/hr. In other studies, ESR was elevated in 88% to 92% of osteomyelitis patients on admission, and the rate of positive test and median or mean ESR value depended on whether there patients had the acute, subacute or chronic form.[4,37] The fact that an ESR  $\geq 40$  mm/hr only had a positive predictive value of 26% in our study confirms that ESR is an unspecific marker for osteomyelitis.[41]

Twenty-six percent of our acute osteomyelitis patients had a positive blood culture, which was lower than in other studies, at 36% to 74%. However, these studies partly recruited patients on the basis of a positive blood culture.[4,19,35,38,39] Blood cultures can only be positive if there is bacteremia at the time the blood is drawn and if sufficient blood is examined. [42,43] In our study, the amount of blood examined for bacteria may have been insufficient. In another study, negative blood culture was found in osteomyelitis patients with small bones and/or non-staphylococcal disease.[42] In line with other studies, *S. aureus* was the most common microbe in our study.[2,4,38] None of our subacute osteomyelitis patients had a positive blood culture. The presence of a positive blood culture has not been described in other studies.[5,37,44]

We classified osteomyelitis patients with disease duration of 14 days or more as subacute osteomyelitis, a definition also adopted in other papers.[4,5] In 69% of these patients, the MRI showed signs of a subacute process.[29,45,46] One of our patients had sequester on admission, a sign of chronic osteomyelitis.[29] In a study by Erdman *et al*, 93% of pediatric and adult osteomyelitis patients (disease duration of more than four weeks) had MRI signs of a subacute process.[14] This could indicate that some patients take more than 14 days to develop subacute MRI signs, or that not all patients develop them.

Why is doctor's delay so common in subacute osteomyelitis? In the acute osteomyelitis patients concomitant septic arthritis was rare however, elevated body temperature and acute phase reactants were more common. Hence these patients seemed to appear more ill. The subacute osteomyelitis patients tended to be older and it is possible that parents and doctors are less concerned about the signs and symptoms these children present. It would have been

interesting to know whether the acute phase reactants had been more elevated prior to hospital admission. In Norway, CRP is frequently used as a marker of inflammation in primary care. Perhaps more use of ESR could help to identify patients at an earlier stage.

## Conclusion

The incidence of osteomyelitis in Norway remains high. It was particularly common in children under 3 years of age. There appears to be a decrease in the proportion of patients with acute osteomyelitis and of patients with long bone involvement. Subacute osteomyelitis patients have more moderate laboratory results and a different presentation on MRI than acute osteomyelitis patients. A blood culture is insufficient to identify microbes in most patients.

## Abbreviations

WBC: white blood cell count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; MRI: magnetic resonance imaging; ROC: receiver operating characteristics; AUC: area under the curve; JIA: Juvenile idiopathic arthritis; SLE: systemic lupus erythematosus; OR: odds ratio; CI: confidence interval.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

ØR, KH, BF and KOW have contributed substantially to conception, design, analysis, interpretation of data, drafting and revising of the manuscript. EK and TR have evaluated all the MRIs and have substantially contributed to analysis, interpretation of data, drafting and revising. BN and MC have contributed substantially to analysis and interpretation of data and revising of the manuscript. All authors read and approved the final manuscript.

## Additional material

### Additional file 1

#### Table 1

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**TABLE 1. Annual incidence of various types of osteomyelitis\***

	Total		Girls		Boys	
	n	Incidence per 100 000	n	Incidence per 100 000	n	Incidence per 100 000
Total osteomyelitis	34	13.3	19	15.2	15	11.5
Location						
- non-vertebral	26	10.2 <sup>1</sup>	12	9.6	14	10.7
- vertebral	8	3.1	7	5.6 <sup>2</sup>	1	0.8
Age group						
- 0–2 years	14	28.1 <sup>3</sup>	9	37.0	5	19.7
- 3–15 years	20	9.7	10	10.0	10	9.5
Onset type						
- acute osteomyelitis	21	8.2	12	9.6	9	6.9
- subacute osteomyelitis	13	5.1	7	5.6	6	4.6

<sup>1</sup> P = .002 vs. vertebral    <sup>2</sup> P = .035 vs. boys    <sup>3</sup> P = .001 vs. age 3–15  
 \* Admitted between June 1, 2004 and May 31, 2005

TABLE 2. Acute phase reactants on admission as diagnostic tests for osteomyelitis in a cohort of children with acute onset musculoskeletal features

	Osteomyelitis ESR (n=35) CRP (n=36)	Non-osteomyelitis ESR (n=332) CRP (n=388)	Sensitivity %	Specificity %	Positive predictive value %	Negative predictive value %
ESR < 20	6 (17)	199 (60)	17	40	3	82
ESR ≥ 20	29 (83)	133 (40)	83	60	18	97
ESR ≥ 40	19 (54)	53 (16)	54	84	26	95
ESR ≥ 60	5 (14)	23 (7)	14	93	18	91
CRP < 10	14 (39)	257 (66)	39	17	5	75
CRP ≥ 10	22 (61)	131 (34)	61	66	14	95
CRP ≥ 20	18 (50)	99 (26)	50	74	15	94
CRP ≥ 40	9 (25)	55 (14)	25	86	14	93

Values in brackets are %

ESR = erythrocyte sedimentation rate (mm/hr); CRP = C-reactive protein (mg/L)

TABLE 3. Characteristics of patients with osteomyelitis versus patients with other acute onset musculoskeletal features on admission

	Osteomyelitis (n=37)	Septic arthritis (n=7) or infection of skin (n = 19)	P-value vs. septic arthritis or infection of skin	Non infectious arthritis (n=198)	P-value vs. non infectious arthritis	Other (n=168)	P-value vs. other
Girls, no. (%)	19 (51)	8 (31)	NS	81 (41)	NS	82 (49)	NS
Age on admission, yrs	4.3 (1.6-14.9)	2.3 (1.1-4.8)	NS	5.2 (3.1-7.9)	NS	5.5 (3.1-10.1)	NS
Duration of symptoms, days	8 (4-49)	2 (1-6)	<.001	3 (1-14)	.001	5 (1-47)	NS
Duration from first visit by primary care physician, days	3 (0-12)	0 (0-0)	<.001	0 (0-2)	.001	1 (0-3)	NS
ESR	41 (27-52)	43 (13-56)	NS	15 (7-29)	<.001	12 (6-26)	<.001
CRP	21 (5-44)	30 (6-67)	NS	5 (2-18)	<.001	5 (1-16)	<.001

All results presented as median (interquartile range) unless otherwise specified  
P-values < .01 were considered statistically significant  
ESR = erythrocyte sedimentation rate (mm/hr); CRP = C-reactive protein (mg/L); NS = not significant

**TABLE 4. Presenting symptom, clinical examination and bone involvement in 37 patients with osteomyelitis**

<b>Presenting symptom</b>	
Refusal to walk and/or sit and/or a limp	22 (59)
Decreased range of motion and/or localized swelling	9 (24)
Localized joint and/or bone pain	5 (14)
<b>Clinical examination</b>	
Localized tenderness	22 (59)
Localized swelling	15 (41)
Localized temperature increase	6 (16)
Localized erythema	5 (14)
<b>Involvement of bones</b>	
Single bone involvement	27 (73)
Long bones <sup>1</sup>	16 (43)
- epiphysis/epiphyseal plate	8 (21) / 6 (16)
- metaphysis/diaphysis	13 (35) / 11 (30)
Craniofacial	1 (3)
Upper extremities	2 (5)
Columna	9 (24)
Pelvis	3 (8)
Lower extremities	22 (59)
- Femur, tibia or fibula	12 (32)
- Foot	10 (27)

Values are no. of patients (%)

<sup>1</sup> Tibia (n = 6), femur (n = 4), fibula (n = 2), phalange (n = 2), humerus (n = 2), clavicae (n = 1)

**TABLE 5. Characteristics in 24 acute and 13 subacute osteomyelitis patients on admission**

	Acute osteomyelitis	Subacute osteomyelitis	P-value
<b>Patient characteristics and laboratory tests</b>			
Girls	12 (50)	7 (54)	NS
Age, yrs	2.7 (1.4–8.2)	10.0 (1.7–12.1)	NS
Duration from first visit by physician until first visit to hospital, days	2 (0–5)	63(20–93)	< .001
Temperature (°C)	37.7 (37.0–38.3)	37.0 (37.0–37.2)	.007
ESR (mm/hr)	44 (36–53)	22 (12–46)	.012
CRP (mg/L)	27 (7–50)	6 (4–21)	.019
WBC (x 10 <sup>9</sup> cells)	12 (8–13)	8 (7–9)	.008
Neutrophils (x 10 <sup>9</sup> cells)	7 (5–8)	4 (3–5)	.003
Platelet count (x 10 <sup>9</sup> /L)	366 (287–444)	362 (289–423)	NS
Concomitant septic arthritis	3 (13)	0 (0)	NS
<b>MRI findings</b>			
Increased signal and/or thick synovia	6/22 (22)	5/13 (38)	NS
Subacute process on MRI	6 <sup>1</sup> /22 (27)	9 <sup>2</sup> /13 (69)	.013
<b>Microbiology</b>			
Positive bacterial culture	11 <sup>3</sup> /23 (48)	4 <sup>4</sup> /12 (25)	NS
- Blood	6 <sup>5</sup> /23 (26)	0/11 (0)	NS
- Bone	4 <sup>6</sup> /6 (67)	4 <sup>7</sup> /7 (57)	NS
- Synovial fluid or soft tissue abscess	3 <sup>8</sup> /4 (75)	0/1 (0)	NS

Values are the median, (interquartile range) or the number of patients (%)

<sup>1</sup> Sharp interface between normal and diseased bone marrow (n = 6), rim of low signal intensity (n = 5), bone cyst (n = 2), and periosteal inflammation with abscess (n = 1). Four of the patients had MRI conducted more than 14 days after the onset of symptoms.

<sup>2</sup> Sharp interface between normal and diseased bone marrow (n = 9), rim of low signal intensity (n = 6), bone cyst (n = 5), periosteal inflammation (n = 2), sclerosis or fibrosis (n = 2), and sequester (n = 1).<sup>3</sup> *S. aureus* (n = 6), *S. pneumonia* (n = 2), *S. pyogenes* (n = 2), *Kingella kingae* (n = 1) <sup>4</sup> *S. aureus* (n = 3), *S. oralis* (n = 1) <sup>5</sup> *S.*

*aureus* (n = 4), *S. pneumonia* (n=1), *S. pyogenes* (n=1) <sup>6</sup> *S. aureus* (n=2), *Kingella kingae* (n=1), *S. pyogenes* (n=1) <sup>7</sup> *S. aureus* (n=3), *S. oralis* (n=1) <sup>8</sup> *S. pneumonia* (n=1), *S. pyogenes* (n=1), *S. aureus* (n=1)  
 Two of the nine vertebral osteomyelitis patients had positive cultures for *S. aureus*

Acute osteomyelitis: a history of less than 14 days at the time of admission.

Subacute osteomyelitis: a history of 14 days or more at the time of admission.

ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; WBC = white blood cell count; MRI = magnetic resonance imaging